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Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A cohort study, 2018 – 2021

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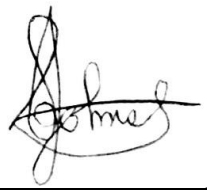
Declaration

I, Leigh Clare Johnston, declare that this Research Report is my own unaided work. It is being submitted for the Degree of Masters of Science in Field Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of the candidate)

29th day of December 2023_

Contributions to the Paper

Leigh Clare Johnston, Dr. Patrick Ngassa Piotie, Ms. Sandhya Singh, and Dr. Alex De Voux conceived the presented idea. Dr. Innocent Maposa helped to develop the methods, assisted with the technical side of the analysis, and verified the analytical methods. Dr. Patrick Ngassa Piotie, Dr. Lazarus Kuonza, Dr. Alex De Voux and Ms. Sandhya Singh supervised the entire work. All authors discussed the results and contributed to the final manuscript.

Dedication

Thanks to my most patient and supportive husband and children.

And in loving memory of my mother, whose belief in me, helps me still believe,

Lynette Johnston

1955 – 2021.

Presentations and Publications

I presented the findings of this study at:

- NICD Epidemiology Forum- 12th April 2023 (12h00 – 13h00)
- At an internal meeting with the CCMDD- 8th May 2023 (13h00 – 14h00)
- Oral presentation at the 8th AFENET conference in Mombasa, Kenya- 5th – 10th November 2023

The findings of this study are yet to be published. The article in submissible format (Chapter Two) has been submitted to the African Journal of Primary Health Care & Family Medicine and is being reviewed.

Abstract

Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A cohort study, 2018 – 2021.

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Background: In South Africa, type 2 diabetes mellitus (T2DM) is a growing public health problem, thus, by 2030, 50% of T2DM patients, receiving treatment, must achieve optimal glycaemic control (haemoglobin A1c (HbA1c) ≤7%). The CCMDD (Central Chronic Medicines Dispensing and Distribution) programme allows glycaemically-stable patients to collect their medication from community-based pick-up points. While the CCMDD is a large public health programme, there is a paucity in stakeholder's knowledge of T2DM patients glycaemic control over time. We determined glycaemic control for CCMDD-enrolled T2DM patients in eThekwini, South Africa from 2018-2021, as well as the rate and predictors of becoming sub-optimally controlled.

Methods: We performed a cohort study, linking HbA1c data from the National Health Laboratory Service to CCMDD-enrolled patients in eThekwini, South Africa from 2018–2021. We included patients optimally controlled at their baseline HbA1c, and having ≥1 repeat test available. We used Kaplan Meier analysis to assess survival rates and Cox regression to determine associations between time to sub-optimal control (HbA1c >7%) and several factors. Adjusted hazard ratios (aHR), 95% confidence interval (95% CI), and p-values are reported.

Results: Of 41145 T2DM patients enrolled in the CCMDD, 7960 (19%) had an available HbA1c result over the study period. A quarter of patients (2147/7960; 27%) were optimally controlled at their baseline HbA1c. Of those controlled at baseline, 695 (32%) patients had a repeat test available, with 35% (242/695) changing their status to sub-optimal control. Patients prescribed dual-therapy had a higher risk of sub-optimal glycaemic control (aHR: 1.503; 95% CI: 1.16–1.95; p-value=0.002) compared to those on monotherapy. HbA1c testing frequency per national guidelines (aHR: 0.46; 95% CI: 0.24–0.91; p-value=0.024) was associated with a lower hazard of sub-optimal glycaemic control.

Conclusions: HbA1c monitoring, in line with testing frequency guidelines, is needed to flag sub-optimally controlled patients who become ineligible for CCMDD enrolment. Patients receiving dual-therapy may require special consideration. Addressing these shortfalls can assist planning and implementation to achieve 2030 targets.

Keywords: Type 2 diabetes; glycaemic control; CCMDD programme; SEMDSA guidelines.

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Definitions

Based on IDF definitions(1).

Fasting plasma glucose (FPG): A measure of blood glucose concentration after fasting (no caloric intake for 8 hours).

Glucose: The main sugar absorbed by the body for energy expenditure and stored for future use. It can only be used by cells with the action of insulin.

Random plasma glucose (RPG): A measure of blood glucose concentration that can be taken at any time of day, regardless of the time since the last meal.

Glycated haemoglobin A1c (HbA1c): Refers to glycation of proteins, which is a secondary event to high blood glucose and the haemoglobin that glucose binds to. It tests the average blood glucose over a two to three-month period.

Low-density lipoprotein (LDL) cholesterol: LDL is one of two lipoproteins, together with high-density lipoproteins (HDL). LDL constitutes most of the body's cholesterol. High levels of LDL cholesterol are associated with an increased risk of heart disease and stroke (2).

Nomenclature

ARV	antiretroviral
BP	blood pressure
CAD	coronary artery disease
CDW	Central Data Warehouse
CHW	community health workers
CI	confidence interval
COVID-19:	coronavirus disease of 2019
CVD:	cardiovascular disease
DALY:	disability-adjusted life year
FPG:	fasting plasma glucose
GP:	Gauteng Province
HbA1c:	haemoglobin A1c (glycosylated haemoglobin)
HIV:	human immunodeficiency virus
HPT:	hypertension
IDF:	International Diabetes Federation
IQR:	inter-quartile range
KZN:	KwaZulu-Natal
LDL:	low-density lipoprotein
LMIC:	low to middle-income countries
mg/dL:	milligrams per deciliter
MI:	myocardial ischaemia
mmol/L:	millimoles per liter
MR:	mortality rate
NCD:	non-communicable disease

NCR:	National Cancer Registry
NDoH:	National Department of Health
NHI:	National Health Insurance
NHLS:	National Health Laboratory Service
NSP:	National Strategic Plan
OR:	odds ratio
PH:	proportional hazards
PHC:	primary health care
PLWT2DM:	people living with type two diabetes mellitus
PoC:	point of care
PUP:	pick-up point
SANHANES:	South African National Health and Nutrition Examination Survey
SD:	standard deviation
SDG:	sustainable development goal
SEMDSA:	Society for Endocrinology, Metabolism, and Diabetes of South Africa
SSA:	sub-Saharan Africa
Stats SA:	Statistics South Africa
STG and EML:	Standard Treatment Guidelines and Essential Medicines List
T2DM:	type two diabetes mellitus
TB:	tuberculosis
UK:	United Kingdom
UN:	United Nations
USA:	United States of America
WCPHDC:	Western Cape Provincial Health Data Centre
WHO:	World Health Organization
ZAR:	South African rand

Preamble

This dissertation is divided into chapters.

Chapter One will introduce the study area of diabetes and will draw on existing studies to illustrate the disease burden and risk factors. The importance of monitoring glycaemic control targets, to reduce diabetes-related morbidity and mortality, will be discussed. Additionally, global and national efforts being taken to deal with the rising epidemic will be described. Despite existing policies, multiple studies will be reviewed that reveal that glycaemic control in South African type two diabetes mellitus (T2DM) patients remains largely sub-optimal.

Chapter Two will be a manuscript in a submissible format, based on the formatting guidelines from the African Journal of Primary Health Care and Family Medicine. This chapter will focus on presenting the methods, results, and discussion for study objectives one and four.

Chapter Three will contain extended methods pertaining to the above objectives, as well as objectives two and three.

Chapter Four will contain extended results for objectives one and four, as well as presenting the results for objectives two and three.

In Chapter Five the findings will be discussed and compared to previous literature. Conclusions will be drawn and recommendations will be made.

CHAPTER 1 – INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

This chapter will introduce the area of Type two diabetes mellitus (T2DM) research. It will outline the epidemiological background and disease burden both globally, and in the South African context. Additionally, the background will describe risk factors related to T2DM. It further introduces recommendations for monitoring glycaemic control and talks to recommended targets for optimal glycaemic control to reduce diabetes-associated mortality and morbidity. Furthermore, it will include a literature review focusing on international and national policies and targets for improved glycaemic control. The Central Chronic Medicine Dispensing and Distribution (CCMDD) programme will be introduced. Previous South African studies that have investigated glycaemic control among T2DM patients will be discussed. The problem statement will highlight the gaps in the current literature; namely, the lack of cohort studies looking at glycaemic control status for CCMDD-enrolled T2DM patients, at enrolment and beyond. Finally, the chapter will describe the present studies' justification, research question, the overall study aims, and the objectives.

1.2 BACKGROUND

Diabetes is a metabolic condition of a chronic nature, characterized by raised blood glucose levels, and is caused by the body not producing sufficient insulin (i.e. insulin deficiency) and/or being unable to efficiently utilize the insulin it produces (i.e. insulin insensitivity or resistance) (1–4). Type one diabetes is genetic in nature and typically presents at younger ages whereas T2DM is largely related to lifestyle factors, and while historically linked to older age, it is now also occurring more frequently in younger age groups (1,4,5). T2DM makes up 90% of the reported cases of diabetes (1).

1.2.1 The burden of T2DM:

A global perspective

Global estimates for diabetes prevalence are on the rise. In 1980, 153 million people were living with diabetes, which ballooned to 347 million in 2008 (6). The most recent 2021 estimates from the International Diabetes Federation (IDF) placed the burden of people living with diabetes at 537 million, representing 10.5% of the global population. The IDF further predicts numbers to

reach 643 million and 783 million by 2030 and 2045, respectively (1). Worldwide, in 2021, over 6.7 million deaths among adults, aged 20–79 years, were attributed to diabetes or to diabetes-related complications (1), equating to 12.2% of total deaths in this age group (1). Thus, exceeding deaths related to human immunodeficiency virus (HIV)/ Acquired immunodeficiency syndrome (AIDS), tuberculosis (TB), and malaria combined in 2015 (4). Diabetes was estimated to directly cost 966 billion USD in 2021; a 316% increase since the estimate of 232 billion USD, 15 years previously (1). Additionally, there is an indirect economic burden associated with diabetes. As 75% of those with diabetes are of working age and experience increased absenteeism and loss of productivity (1,5).

A South African perspective

Low- to middle-income countries (LMIC) make up 80% of diabetes cases (1). Africa is predicted to bear the greatest brunt with a projected 134% increase in diabetes prevalence from 2021 to 2045 (1). Of the Sub-Saharan Africa (SSA) countries, South Africa has reported the highest prevalence of diabetes (4), estimated at 11.4% by the IDF in 2021(1). Thus equating to 4.2 million people living with diabetes (1). In 2018, Statistics South Africa (Stats SA), listed diabetes as the second leading underlying natural cause of mortality overall (fourth for males and first for females) (7).

1.2.2 Risk factors for T2DM

Globally, commonly cited risk factors for T2DM are modifiable lifestyle factors such as the use of tobacco, poor diet, obesity, and a lack of physical activity (1,8). Additionally, non-modifiable factors such as age, gender, family history, and life course events drive T2DM (9).

In the South African context, there are also complex and less easily modifiable risk factors at play (4,8,9). These include social and commercial determinants of health, such as low socioeconomic status and poverty, as well as rapid urbanization, with the associated changes to a Westernised diet and sedentary lifestyles (8,10). T2DM is more prevalent in women than men at 16.8% and 12.4%, respectively (11). This disparity by sex is thought to be linked to the predisposition of obesity in South African females (8). Differences by ethnicity have been documented with prevalence among the Black African, Coloured, and Indian populations at 11.3%, 23.7%, and 33.6% respectively (11,12).

Furthermore, in South Africa, the complex setting of a quadruple disease burden with prevalent HIV and TB, adds an additional layer of complexity as T2DM interacts with these diseases. T2DM has been linked to a two to three-times increased risk for TB infection and is associated with increased TB treatment failure and death (13). HIV infection and treatment also increase the risk for T2DM (4). Both HIV antiretroviral (ARV) protease inhibitors and nucleoside reverse transcriptase inhibitors have been causally linked to diabetes (14). Additionally, ARVs and advancing TB treatment have led to increased life spans of those living with the conditions, and with increasing age, non-communicable disease (NCD)s are developing more frequently (14). Hypertension has also been identified as a common comorbidity in people living with type 2 diabetes mellitus (PLWT2DM), with an 87% prevalence noted in a facility-based study in KwaZulu-Natal (KZN) from 2019 (15). The risk of all diabetes-related complications increased for those with a hypertension comorbidity (15).

1.2.3 Sub-optimal glycaemic control in T2DM

Guidelines for the monitoring of glycaemic targets in T2DM care

Setting glycaemic targets for T2DM care, serves to prevent microvascular and macrovascular complications in those living with T2DM, by ensuring that patients are not undertreated (4). Additionally, effective monitoring allows for early intervention, with resulting glycaemic control, which can substantially decrease morbidity and mortality related to T2DM (1).

The 2017 Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) and the 2020 South African Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for primary health care (PHC) and hospital-levels, have published guidelines for T2DM care and glycaemic monitoring (4,16,17). Provinces use the STG and EML guidelines to govern their clinical care. Both the STG and SEMDSA guidelines recommend using haemoglobin A1c (HbA1c) as a monitoring tool as it captures glycaemic control over two to three months (1,4,16,17). And in both, a target level of $\leq 7\%$ is considered optimal (4,16,17). Diagnostic values for diabetes are 6.5% or higher, thus HbA1c of below 7% is considered excellent (1,5).

For those with stable glycaemic levels, HbA1c is recommended to be monitored six monthly (SEMDSA guideline) or annually (STG/EML guideline) (4,16,17). For those who are not in the target range or who have had a change in their T2DM management, monitoring is recommended three to six-monthly (4,16,17). The SEMDSA guidelines also include measures for

cardiovascular risk factors such as dyslipidemia, and hypertension as T2DM is an additional risk factor for macrovascular complications causing coronary artery disease (CAD) and cardiovascular disease (CVD) (4). In T2DM, serum lipids are commonly characterized by increased triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol (4). However, studies have repeatedly revealed that reducing calculated low-density lipoprotein (LDL) cholesterol, with statins, in T2DM patients decreases the risk of CVD (4). Thus SEMDSA and STG guidelines recommend that when a patient is first diagnosed with diabetes, serum lipids be checked (i.e. total cholesterol and triglyceride levels initially, followed by a 10-hour fasting lipogram, including total cholesterol, triglycerides, calculated LDL and HDL cholesterol, if the results were elevated) (4,16). Guidelines recommend the lipogram be repeated annually, if the results are within recommended ranges, and 3-monthly if not (4).

Complications associated with sub-optimal glycaemic control in T2DM patients

T2DM is linked directly to retinopathy, neuropathy, and nephropathy as well as causing an increased risk for the development of cardiac and cerebrovascular disease (3). Microvascular disease, linked to retinopathy, neuropathy and limb-threatening ischemia, and resultant amputations, all substantially affect quality years of life lost, disability-adjusted-life-years; and add to burgeoning costs to the health system (18). An HbA1c reading of more than 7.5% increases the risk of microvascular disease by 37% (19) and by 2–4 times for CVD and stroke (20). For each incremental decrease of 1% in HbA1c, the risk for amputation, heart attack, stroke and death related to diabetes decreases by 43%, 14%, 12%, and 21% respectively (19).

The estimated cost for the public health sector, of both those diagnosed and undiagnosed, in 2018 was ZAR (South African rand) 21.8 billion. By 2030, the projected costs are a staggering ZAR 35.1 billion (18). Of the 2030 estimate, 49% of costs are attributed to managing T2DM complications. Which are in turn, linked to sub-optimal glycaemic control and are essentially preventable (18).

Furthermore, within the current context of the coronavirus disease of 2019 (COVID-19) pandemic, T2DM has been linked to more severe disease course and increased mortality rates (21,22). In the United States of America (USA), hyperglycaemia was found to be predictive of increased COVID-19 mortality rates (MR) at 28.8% compared to 6.2% in those without diabetes (22). Furthermore, of the patients admitted with hyperglycaemia, those who were uncontrolled

had a 41.7% MR compared to a 14.8% MR in those who were controlled (22). Locally, data from the national COVID-19 hospital surveillance system, DATCOV, estimated that of the COVID-19 patient admissions, 29% had diabetes as a comorbidity, and that NCD comorbidity was associated with increased mortality (23). As such, it is critical to monitor and achieve glycaemic targets to decrease disease course severity and death rates (21).

1.3 LITERATURE REVIEW

1.3.1 Global NCD Targets and Policy Landscape

There is a global concern about the increasing burden of NCDs, however, the management of NCDs is a complex undertaking (6). The United Nations (UN) High-level Summit for the prevention and control of NCDs in 2011, raised awareness of the disease burden and the socioeconomic consequences of NCDs, including T2DM; and prioritized tackling NCDs (24,25). The World Health Organization (WHO) published a Global Action Plan for the Prevention and Control of NCDs 2013–2020 (26,27). In 2015, the SDG targets for 2030 were created. Target 3.4 (Good Health and Well-Being) spoke to reducing premature mortality due to NCDs by a third.

To facilitate member countries to achieve SDG 3.4 by 2025, the WHO published “best buys” for tackling NCDs in 2017 (26). The “best buys” are cost-effective and feasible policy options that are designed to have maximal public health impact (24,26). They include addressing key risk factors for NCDs, namely, reducing the use of tobacco and alcohol, as well as, unhealthy diets and insufficient physical inactivity (26). They also recommend up-scaling the early detection of NCDs; strengthening health system capacity and access to essential medication and digital technology; and promoting universal health coverage and person-centered health care (26). In terms of diabetes, specifically, it also recommends preventative foot care, retinopathy screening, and, critically, achieving optimal glycaemic control (26).

The WHO Global Diabetes Compact in 2021 further recommended quality care through the achievement of glycaemic control targets (28). On the 28th of May 2022, the WHO newsroom released the global targets for diabetes, following the 75th World Health Assembly. The targets aimed to achieve 80% of people living with T2DM (PLWT2DM) being diagnosed, and 80% of PLWT2DM achieving glycaemic control by 2030 (29). In addition, to prevent macrovascular

complications, it includes the targets of 80% of PLWT2DM being controlled for their blood pressure (BP); and 60% of PLWT2DM, over 40 years of age, receiving statins (29).

Following the 76th World Health Assembly in May 2023, the "best buys" were expanded, to include a greater menu of intervention and policy options for member states of all income levels (30). Some of the expanded policy options include increased tax and advertising bans for tobacco and alcoholic beverages, as well as, reformulating unhealthy foods and enforcing nutritional labeling of food items, protecting children from advertising of harmful food and beverages, and promoting breastfeeding (30).

1.3.2 South African NCD Targets and Policy Landscape

The formation of the Directorate for Chronic Diseases, Disability, and Geriatrics, within the NDoH, in 1996, has led to multiple national guidelines to prevent and control NCDs in South Africa (24,31). The SA National Department of Health (NDoH) introduced several population-wide initiatives to address the NCD burden by addressing behavioral risk factors, such as population-level legislative control measures for sugar in beverages, tobacco, salt, trans-fats, and limited programmes targeting physical activity (24,31,32). These have proven partially effective (24,31,32), with stronger evidence for the effectiveness of both the tobacco and sugar legislative measures (**Table 1.1**).

Table 1.1*: Legislative control measures to curb non-communicable diseases in South Africa*

Control Measure	Legislation	Proof of Impact
Tobacco Products Control Act of 1993 (with amendments in 1999 and 2007)	Increased taxation, health warnings to be displayed on tobacco products, and banned sales to under-16s (24,33)	Resulted in a reduction in smoking of 26% between 1993 and 2000 (34).
Health Promotion Levy in 2018	Introduced a sugar-based tax of 10% on beverages sweetened with sugar (24,35)	Reductions, in daily household consumption of sugar by 51%, in calories by 52%, and in volume consumed by 29% (36). Manufacturers reformulating their products (36). Greatest effect was in lower-income households suggesting a public health benefit for those most at risk and least able to afford healthcare (35,36).
National Sport and Recreation Strategic Plan (2012 – 2016) & the Sports Charter	Aimed to increase physical activity in the general population by 10% by 2020. To improve equitable access to safe and secure sporting facilities (24,37).	None of note
Liquor Act passed in 2003	Reducing the harmful use of alcohol, and the associated social	Sales in unregistered outlets remain uncontrolled, even for

	behaviors, and additionally prohibiting sales to those under-18s, while still sustaining the liquor industry (24,38).	minors, and there have been minimal improvements in public health as a result (24).
The salt regulation legislation (2016 and 2019)	To lower salt content in processed foods (24).	Monitoring of compliance has been limited (24).

The South African Department of Health's National Strategic Plan (NSP) for the Prevention and Control of Non-Communicable Diseases (2022–27), built on existing policy and legislation, and developed further guidelines for NCDs (24). In line with SDG targets for 2030 and the National Health Insurance (NHI) goals (23), it aimed to reduce premature mortality (death in those under 60 years) by 25%, and to proportionally increase those controlled for diabetes by 30% (39). Additionally, it set additional goals for 2030, namely, achieving 90% of people living with type two diabetes mellitus (PLWT2DM) diagnosed, 60% of those diagnosed receiving treatment, and 50% of those receiving treatment achieving glycaemic control (39).

The NSP strategy relies on major reforms of the SA Health Care System and cross-cutting implementations across the NHI, Primary Health Care, Schools Health Programmes, and Human Resource Development programmes to support non-communicable disease prevention and control (32,39,40). Primary care interventions include the Primary Health Care Re-engineering policy and, the Integrated Chronic Disease Management approach. These sought to mobilise and build on existing skills in ward-based outreach teams and community health workers (CHW), historically used for HIV/AIDS home-based management; and sought to extend CHW's scope to include NCD screening and education to deliver integrated NCD services (32,40,41).

Additionally, community-based services were established, in terms of NCD support groups and community-based medication delivery mechanisms (32,42). Thus addressing commonly cited barriers to care for PLWT2DM in South Africa, such as promoting easier access to medication, by negating long waiting times, medication stock-outs, and inaccessible clinics (32,42).

The Central Chronic Medicine Dispensing and Distribution Programme

The CCMDD programme, situated in the NHI programme, was launched by NDoH in 2014 (43,44). It aimed to improve access to medication and to provide affordable, quality health care to all South Africans (43,44). The CCMDD allowed stable HIV and NCD patients to collect their chronic medications from community-based pickup points (PuPs), such as independent pharmacies, adherence clubs, and Smart Lockers every second month (43) (***Figure 1.1)***. In addition to promoting medication accessibility, it also improved adherence, reduced

transportation costs for patients, decongested clinics, and relieved overburdened staff to allow for improved quality of care (32,45).

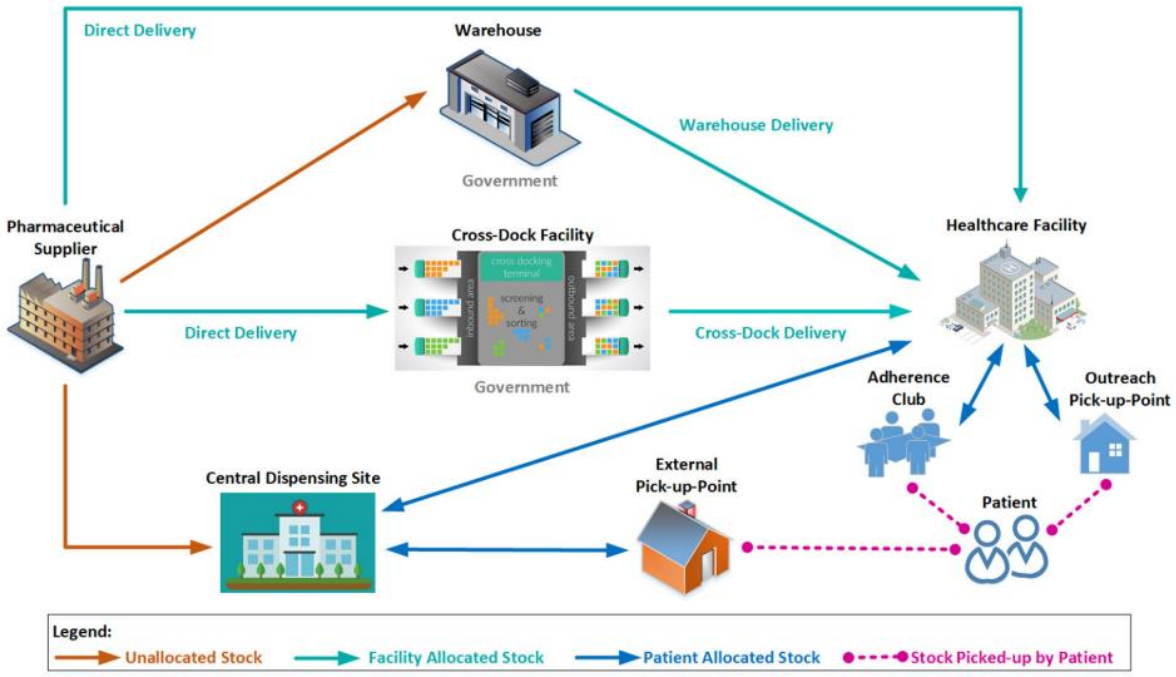

Figure 1.1: *Distribution pathways within the CCMDD* (44)

T2DM patients were eligible to be enrolled into CCMDD if they were 18 years or older, able to give consent, and were stable for their condition (43). Being stable on medication was defined as having two consecutive normal fasting plasma glucose (FPG) readings of less than 7 mmol/L (43). Patients that require frequent clinical follow-ups for another condition, such as TB, are excluded from the programme; as CCMDD-enrolled stable patients only attend their clinics biannually for follow-up and to renew their prescriptions (43). Other non-stable patients with T2DM, as per the STG, attend clinics, quarterly (4,16).

By 2018 an 88% reach had been achieved and 94.6% of facilities in the districts involved were represented (43). Of the 2 069 039 active patients in the programme, 24% were collecting medication for chronic disease alone (43). It was hailed a success as 35% of registered patients were using external PuPs, rather than queuing at clinics, and patient retention in the programme was 70% (43). However, there is currently no monitoring and evaluation in place for the glycaemic control of T2DM CCMDD-enrolled patients over time. As such, there is no mechanism in place, to assess patients' continued eligibility (i.e. remaining stable for their condition), after enrolment.

1.3.3 Rule of Halves Framework for Diabetes and Diabetes Care Cascades

The Rule of Halves is well known in NCD epidemiological circles, since its first use, in 1974, to describe the unmet care for non-insulin-dependent PLWT2DM in the USA (46). Five decades later, the Rule of Halves framework is still thought to hold true for diabetes in describing the unmet need for care within the care cascade. That is, half of those with T2DM get diagnosed, only half of those diagnosed with T2DM get treatment and only half of those treated go on to achieve recommended glycaemic targets (***Figure 1.2)*** (46). Napier et. al. (2017) also included a fifth tier, where 6% of those achieving glycaemic targets are free from diabetes-related complications (47).

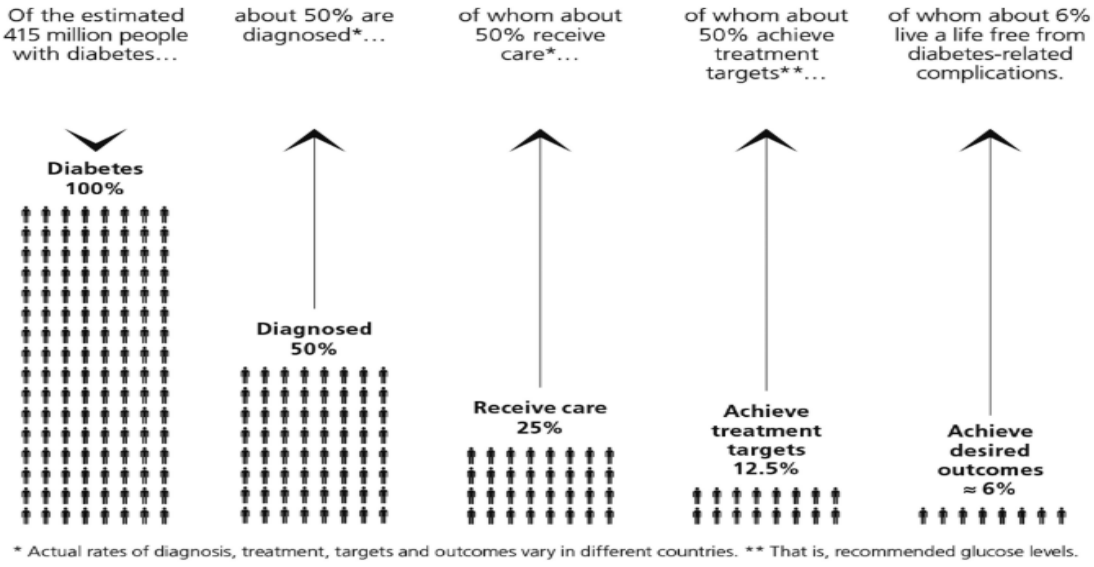

Figure 1.2: *The Rule of Halves Theoretical Framework* (47)

Categorisation across the continuum of care, in this manner, can pinpoint at which points in the cascade of care the need for care is unmet (48). Cascades of care have been successfully used, in HIV/AIDs management. The 95-95-95 UN cascades of care targets, successfully drove global strategies to achieve improved HIV/AIDs care and management (49). This approach has been followed for T2DM with some success, however, international targets have not been defined (49).

Internationally, more developed countries, such as Copenhagen, in 2017, have surpassed the 50% mark, for those diagnosed with diabetes (at 74%) and for those diagnosed being treated (at 90%); however, they fell shy in terms of those achieving glycaemic control (at 40%–60%). Of those

who were optimally controlled, there was a complication rate of 11% for retinopathy and 25% for macrovascular events (50). Similarly, in the USA in 2019, 94% of those with diabetes were linked to care and 64% of those had achieved optimal glycaemic control (51).

In less developed countries, where medication and health care is not always free, the above targets may be difficult to achieve. This was evident in a population-based study in South Africa, by Stokes et al (2017), using data extracted from the South African National Health and Nutrition Examination Survey (SANHANES: 2011–2012). They found that 40% of those with diabetes had been diagnosed, with 94% of those diagnosed receiving treatment and of those treated 51% had achieved optimal glycaemic control (48). This equates to 19% of all of those with T2DM achieving optimal glycaemic control. Thus highlighting a gap in terms of effective management (48). To our knowledge, this study provides the only baseline values, at a national-level, for the care cascades in South Africa. Without more recent baseline estimates, the NDoH has no accurate reference point to gauge their progress towards their 2030 NSP goal of improving the proportions of those controlled for their diabetes by 50% (39).

1.3.4 South African Studies on Glycaemic Control

At facility-level, several studies on glycaemic targets in T2DM patients in South Africa, between 1999 and 2021, have looked at proportions of optimally controlled patients, based on recommended glycaemic targets (HbA1c <7%), through retrospective patient chart audits (52–58). Five have been at either secondary or tertiary-level facilities, and observed proportions of those optimally controlled varying from 20.1% at Umtata General Hospital (1999), 30.7% at Gauteng province (GP) academic hospitals (2009) (52,53), to 19.3% at Hillbrow Clinic (2017), 15.4% in Port Shepston Hospital (2017) (54,58), and 15.3% at Helen Joseph Hospital in 2020 (55). Two studies were based at PHC clinic level, in Tshwane. A study by Webb, Rheeder and Van Zyl (2015) found 27% of diabetic patients were optimally controlled, and Ngassa Piotie et. al. (2021) found 29% were optimally controlled (56,57). The larger proportions of sub-optimal control observed at secondary and tertiary level hospitals, compared to PHC level, can be explained by patients who are more complicated in nature (i.e. those with more complications, comorbidities, or being difficult to manage) being up-referred to larger facilities for more specialised care. Once better managed, patients are stepped back down to PHC clinics (55).

Of further concern, Ngassa Piotie et. al.'s findings, of only 29% of T2DM patients being optimally controlled, occurred in patients enrolled in the CCMDD (57). As patients have to have glycaemic control (from two consecutive FPG readings) as a prerequisite for enrolment into the programme, this was an alarming figure (57). The study concluded that despite medication being more accessible, other barriers to the achievement of glycaemic control targets existed and further investigation into potential explanatory factors, by means of a cohort study, was recommended (57).

1.4 PROBLEM STATEMENT

The WHO recommends that 80% of PLWT2DM achieve recommended targets for glycaemic control (29). The SA NSP for NCDs aims to achieve 50% of those receiving treatment, attaining glycaemic control by 2030 (39). Previous studies consistently report small proportions of T2DM patients reaching glycaemic targets (15.3%–30.7%), across primary and tertiary levels of care, and across provinces in South Africa. However, they have been largely cross-sectional patient record reviews. As such, there may have been information bias due to incompleteness and poor data quality (52–55,57,58). Additionally, there is no reliable central data repository for T2DM in South Africa. Only one study has looked at glycaemic control among T2DM CCMDD-enrolled patients (57). They concluded, that despite medication being more accessible, glycaemic control was poor; thus recommending a cohort study to investigate other explanatory factors (57). While the CCMDD captures demographic and prescription information on patients with stable T2DM, it does not include clinical measures such as HbA1c and LDL. The National Health Laboratory Services (NHLS)'s central data warehouse (CDW), has the majority of this information available, as the single public health care laboratory provider in KZN.

A gap exists in that there are no robust cohort studies of district-level data available to confirm the proportions of CCMDD-enrolled patients, on treatment for their T2DM who are achieving glycaemic control (**Figure 1.3**). As such, the NDoH has no recent, accurate reference point to determine the magnitude of the unmet need for diabetes care for CCMDD-enrolled patients, and are unable to gauge their progress towards the NSP targets. Additionally, data is pauce for factors associated with sub-optimal glycaemic control among CCMDD-enrolled T2DM patients.

1.5 JUSTIFICATION

Merging and enhancing the CCMDD patient information with NHLS clinical data provides a unique opportunity to retrospectively follow a cohort of patients retrospectively, accounting for variation in HbA1c over time. This cohort study builds on previous studies to determine glycaemic control within the CCMDD programme. This study also identifies sub-groups at increased risk of developing sub-optimal glycaemic control. Identifying, understanding, and integrating these factors or vulnerabilities into diabetes care would prevent diabetes-related morbidity and mortality and reduce expenses related to uncontrolled T2DM. Findings can enhance existing CCMDD data, assist in monitoring and evaluation, and assist with more targeted interventions. Additionally, the information from this study can assist the NDoH to monitor and evaluate South Africa's progress towards achieving the NSP goals for 2030. Moreover, as no central data repository for T2DM exits in the majority of South Africa's districts and provinces (except for Western Cape), the merging of datasets may reveal if it is possible to estimate whether needs are being met in the care cascade, at district-level, rather than relying on facility-based audits for this information.

1.6 RESEARCH QUESTION

The research question is whether adult T2DM CCMDD-enrolled patients, collecting chronic medication from community PuPs were optimally controlled at baseline and last HbA1c reading, as well as the rate and predictors of becoming sub-optimally controlled, between April 2018 and June 2021, in the eThekwini district, KZN.

1.7 AIM OF THE STUDY

The overall aim was to determine glycaemic control, at baseline and last HbA1c reading, as well as the rate and predictors of becoming sub-optimally controlled for CCMDD-enrolled T2DM patients in eThekwini, South Africa from 2018-2021.

1.8 OBJECTIVES OF THE STUDY

1. To determine proportions of T2DM patients optimally controlled at enrolment into CCMDD by the achievement of the SEMDSA and STG recommended targets for:

(a) baseline (BL) HbA1c and

(b) the SEMDSA target for BL LDL.

2. To determine proportions of T2DM patients optimally controlled at the last recorded test (closest to June 2021) by achievement of the SEMDSA and STG recommended targets for:

(a) HbA1c and

(b) the SEMDSA target for LDL.

3. To determine factors associated with sub-optimal glycaemic control at baseline and last recorded test, in terms of:

(a) demographic factors, (b) intermediate targets for cardiac health, (c) type of treatment, (d) quality of care, and (e) co-morbidities.

4. To determine the time to failure (i.e. the first event of sub-optimal control) and associated predictors (as in objective 3) for developing sub-optimal control.

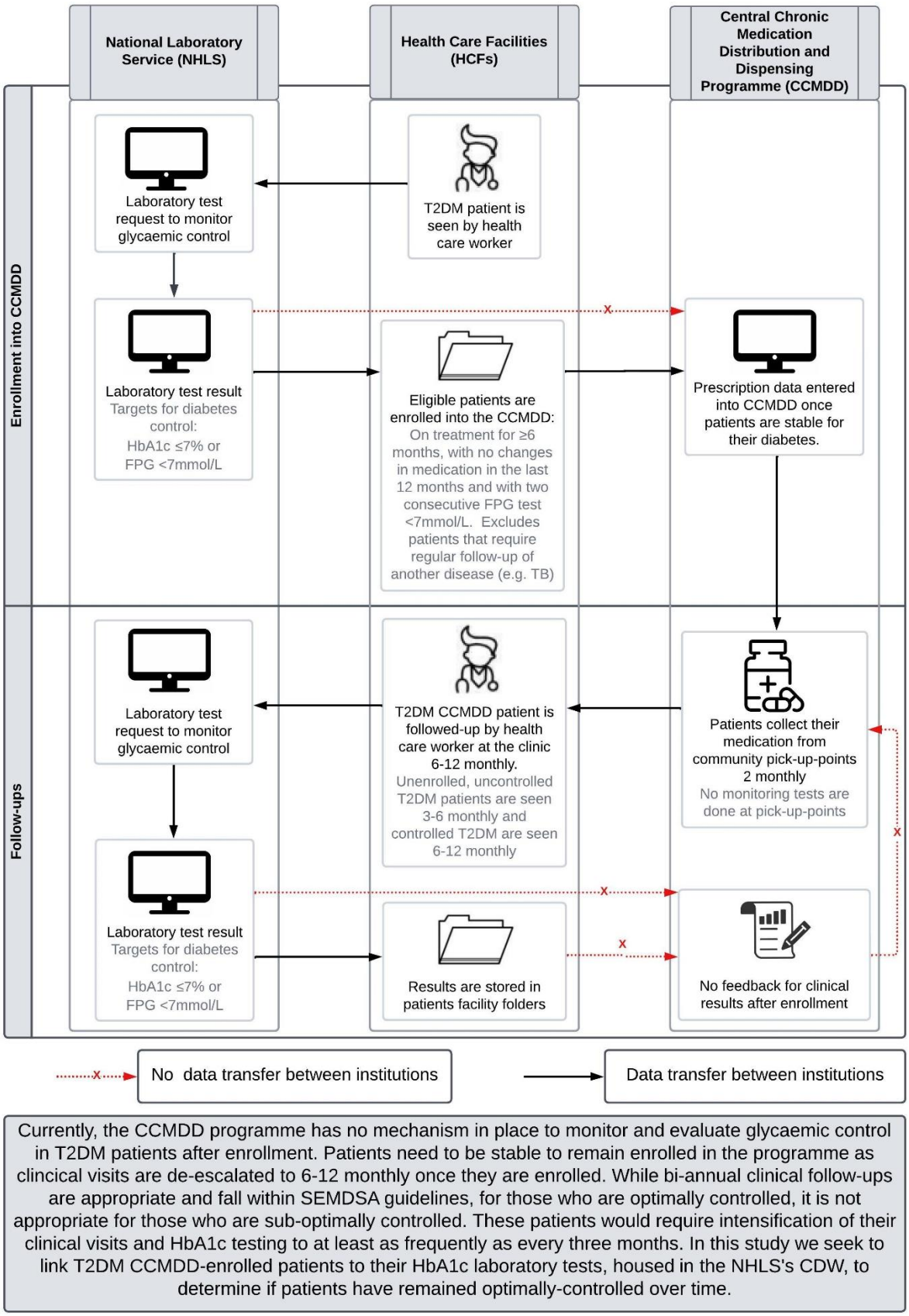

***Figure 1.3**: A diagrammatic summary of the gap between the existing NHLS laboratory and the CCMDD programmes data and the implications on care guidelines.*

CHAPTER 2 – ARTICLE IN SUBMISSIBLE FORMAT

For submission to the African Journal of Primary Health Care & Family Medicine (AOSIS publishing guidelines can be found in **Appendix 9**)

Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A cohort study, 2018 – 2021.

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ABSTRACT

Background: The CCMDD (Central Chronic Medicines Dispensing and Distribution) programme allows clinically stable type 2 diabetes mellitus (T2DM) patients to collect their medication from community-based pick-up points.

Aim: We determined baseline glycaemic control and the rate and predictors of becoming sub-optimally controlled for T2DM CCMDD-enrolled patients in eThekwini, South Africa from 2018- 2021.

Methods: We performed a cohort study for patients enrolled in the CCMDD, in eThekwini, between April 2018– December 2021. We linked glycated haemoglobin (HbA1c) data from the National Health Laboratory Service to CCMDD-enrolled patients allowing a six-month time buffer (i.e. October 2017– June 2022). We selected patients optimally controlled at their baseline HbA1c, and having more than 1 repeat-test available. We used Kaplan-Meier analysis to assess survival rates and extended Cox regression to determine associations between time to sub-optimal control (HbA1c >7%) and predictors. Adjusted hazard ratios (aHR), 95% confidence interval (CI), and p-values are reported.

Results: Of 41145 T2DM patients enrolled in the CCMDD, 7960 (19%) had a HbA1c result available, with a total of 12102 HbA1c tests performed. Twenty-seven percent (2147/7960) were optimally controlled at their baseline HbA1c. Of those controlled at baseline, 695 (32%) patients had a repeat test available, with 35% (242/695) changing to sub-optimal status, with a 25^{th} percentile of survival time of 2.88 years. HbA1c testing frequency per national guidelines was associated with a lower hazard of sub-optimal glycaemic control (aHR: 0.46; 95% CI: 0.24–0.91; p-value=0.024). Patients prescribed dual-therapy had a higher hazard of sub-optimal glycaemic control (aHR: 1.50; 95% CI: 1.16–1.95; p-value=0.002) versus monotherapy.

Conclusions: HbA1c monitoring, in-line with testing frequency guidelines, is needed to alert the CCMDD of patients who become ineligible for enrolment. Patients receiving dual-therapy require special consideration.

Contribution: We identified shortfalls in the CCMDD, and predictors for developing sub-optimal control, that can assist future programme planning and implementation.

INTRODUCTION

Diabetes is the second leading natural cause of death in South Africa (SA),[1] affecting an estimated 4.2 million people.[2] Ninety percent of people living with diabetes have type 2 diabetes mellitus (T2DM), considered a preventable and potentially reversible condition.[2,3] However, prevalence has continued to rise, particularly among women.[1] The growing trend has been fueled by lifestyle factors (e.g. urbanisation, increased consumption of processed foods, reduced physical activity, and obesity); as well as, social and commercial determinants of health.[2,3]

Due to the chronic nature of the disease, people living with T2DM (PLWT2DM), need to monitor their glycaemic levels regularly, thus continuously assessing their disease progression and preventing T2DM-related complications.[2,3] T2DM-related complications include macrovascular diseases (i.e. CVD or stroke) and microvascular diseases (i.e. retinopathy, neuropathy, and nephropathy).[4] Sub-optimal or poor glycaemic control has been linked to a 37% increased risk of microvascular diseases[5] and a 2- to 4- fold increased risk of macrovascular diseases.[6]

Various tests exist to monitor glycaemic control, including, fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) tests. FPG is an indicator of short-term glycaemic levels, and is in constant flux, since it is dependent on factors such as food consumed, stress, or physical activity.[7] HbA1c is a longer-term indicator of glycaemic control, over 2 to 3 months,[7] and is considered the gold standard for glycaemic monitoring by the International Diabetes Federation (IDF).[2] When using HbA1c, sub-optimal glycaemic control, is defined by test readings of >7%.[3,8]

Current guidelines by the Society for Endocrinology, Metabolism and Diabetes South Africa (SEMDSA) recommend HbA1c monitoring three-monthly if control is sub-optimal and six-monthly if control is optimal.[3] The standard treatment guidelines (STG) for primary health care in South Africa recommend three- to six-monthly HbA1c testing if sub-optimally controlled (HbA1c >7%) and 12-monthly testing if optimally controlled (HbA1c ≤7%).[8] Those with sub-optimal glycaemic control require more frequent monitoring, to allow for early corrective actions to achieve optimal control. Early corrective actions help prevent T2DM-related complications, which impose considerate costs to the public health service and social and economic costs to PLWT2DM.[2]

Considering the magnitude of the public health problem posed by non-communicable diseases (NCD) including diabetes, the SA National Department of Health (NDoH) launched the National

Strategic Plan (NSP) for the Prevention and Control of Non-Communicable Diseases 2022–2027, in May 2022.[9] The NSP aimed, among others, to ensure that 50% of those receiving T2DM treatment, achieve glycaemic control by 2030.[9]

Underpinning the NSP, are existing policies, such as, the Primary Health Care Re-engineering policy and, the Integrated Chronic Disease Management approach. These include developing, and mobilising existing community-based services (e.g. support groups and community-based medication delivery mechanisms), to manage NCD patients at community-level.[10,11] The Central Chronic Medicines Dispensing and Distribution (CCMDD) programme is one such initiative and was launched in 2014 by the NDoH.[12] The CCMDD allowed stable HIV-positive and NCD patients to collect their chronic medications from community-based pick-up points, such as independent pharmacies, adherence clubs, and smart lockers every second month.[11,12] Thus, services are decanted to decongest clinics and relieve overburdened staff, allowing for improved quality of care.[12,13] Additionally, the programme addresses commonly cited barriers to accessibility and adherence to medication, such as reducing transportation costs for patients, and negating long waiting times and medication stock-outs at clinics.[12,13]

T2DM patients are eligible to be enrolled into CCMDD if they are 18 years or older, able to give consent, and medically stable.[12] Being stable on medication was defined as having two consecutive normal fasting plasma glucose (FPG) readings of less than 7 mmol/L, being on medication for more than six months, and having no changes to medication in the last year.[12] Non-stable patients with T2DM, as per the STG, attend clinics quarterly,[8] while non-enrolled stable patients[8] and CCMDD-enrolled stable patients attend clinics biannually for follow-up and for prescription renewal.[12]

The CCMDD does not collect clinical data, therefore, there is limited evidence of clinical outcomes over time for patients enrolled in the programme. Merging and enhancing the CCMDD patient information with laboratory data housed in the central data warehouse (CDW) of the NHLS clinical provides a unique opportunity to follow a cohort of patients retrospectively, accounting for variation in HbA1c over time. This cohort study builds on previous studies to determine glycaemic control within the CCMDD programme. This study also identifies sub-groups at increased risk of developing sub-optimal glycaemic control. Identifying, understanding, and integrating these factors or vulnerabilities into diabetes care would prevent diabetes-related morbidity and mortality and reduce expenses related to uncontrolled T2DM. Findings can

enhance existing CCMDD data, assist in monitoring and evaluation, and assist with more targeted interventions. Additionally, the information from this study can assist the NDoH to monitor and evaluate South Africa's progress towards achieving the NSP goals for 2030.

KwaZulu-Natal (KZN), and the district of eThekwini, in particular, have been highlighted by recent research as an area of particular concern for their diabetes disease burden, with eThekwini representing 45% to 55% of newly diagnosed cases in the province.[14,15] To our knowledge, there are no prior studies within the CCMDD, addressing changes in glycaemic control over time in eThekwini, KZN. In this article, we determined the proportions of CCMDD-enrolled patients achieving optimal glycaemic control and looked at factors associated with an increased hazard for developing sub-optimal control.

METHODS

Study design

We conducted a retrospective cohort study to describe HbA1c test results extracted from the NHLS CDW, for all T2DM CCMDD-enrolled patients receiving oral hypoglycaemic medications through the programme between April 2018 and December 2021 in eThekwini, KZN.

Study setting

The study took place in the public health sector in the district of eThekwini in KZN, South Africa.

Data Sources

We sourced our data from the CCMDD and NHLS CDW. The CCMDD has achieved a reach of 88%, with 94.6% of facilities in the districts represented.[12] As such, CCMDD reaches eight community health clinics, 99 clinics, and 13 hospitals within eThekwini. The NHLS is the sole provider of laboratory services for the public health system, serving 80% of the population.[16]

Study participants

The study participants were all T2DM adult (≥18 years) male and female patients enrolled in the eThekwini CCMDD over the study period (April 2018 to December 2021). As this study used

secondary data, no sampling was done. We selected those with non-missing HbA1c data from the NHLS CDW. We allowed a six-month window, for the HbA1c reading from the clinical visit preceding the patient's first CCMDD prescription date, and the last CCMDD prescription date, to be included (October 2017 and June 2022). For the survival analysis, we selected those optimally controlled at their first HbA1c measure and with a repeat HbA1c test/s available between October 2017 and June 2022.

Variables and data management

CCMDD data was provided as an Excel spreadsheet and was exported to STATA version 17 for cleaning and analysis. The CCMDD data included date of birth, sex, healthcare facility, T2DM-related complications, and details of the first and last prescription (medication and prescription dates). The data was checked for errors, inconsistencies, outliers, and missing data. Any duplicate participants and duplicate observations per participant, were identified and removed. Data was transformed from a long to a wide format. This data was sent as an excel spreadsheet to the NHLS gatekeepers, who matched Hba1c test results to the CCMDD line list using the national identity number. The NHLS HbA1c data included the date of the specimen, the date of the laboratory test, and the test name and value. This data was sent back to the primary investigator. The variables for HbA1c test date, the HbA1c result, and the unique patient ID, were used to determine a duplicate HbA1c observation. Data variables were unstrung and formatted as numerical, date values or encode as categorical variables, as was appropriate.

We used HbA1c values from the NHLS merge, which was a continuous measure. We created a binary variable for optimal and sub-optimal control. This study defined glycaemic control as optimal if the HbA1c reading was 7% or less and as sub-optimal for values above 7%. This is per the 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines and the 2020 South African Standard Treatment Guidelines (STG).[3,8] We defined the baseline HbA1c value as the first recorded NHLS value within the study period. For the survival analysis, only those optimally controlled at their first reading in the study period were used, and time-to-failure was calculated for the first change of status to sub-optimal control. We also created a categorical variable from the HbA1c value, where values less than or equal to 7% were optimal, and sub-optimal values were further sub-catagorised as 7.1–8.9%, 9–11.9%, and 12% or more. These categories were chosen *a priori*, based on the literature review.

We calculated age using the "datediff" command to subtract the HbA1c sample collection date from the patient's date of birth. Once calculated, we categorised age in years, in four levels, as follows: 18–39, 40–59, 60–79 and 80 or over. We used these categories as the age data was skewed suggesting nonlinearity. We included the categories 18–39 and 80 or over, despite the relatively fewer values to isolate the aberrant median HbA1c values in these categories.

To manage diabetes, the STG and essential medication list (EML) of South Africa, advise lifestyle modification, followed by progressive pharmacological therapies; starting with monotherapy (i.e. metformin) and are up-scaled to dual-therapy (i.e. metformin and a sulphonylurea agent, namely, glibenclamide or glimepiride), and finally to insulin, if a patient is still sub-optimally controlled or if their disease progresses.[8] We used the "strops" function to identify these medications used for diabetes management. We then used "egen" function to total tags for metformin, glibenclamide and glimepiride for each unique patient ID, to create a categorical variable with three levels, as follows: monotherapy (one oral hypoglycaemic agent prescribed), dual-therapy (two hypoglycaemic agents prescribed) and triple-therapy (three hypoglycaemic agents prescribed) in the same prescription. Since the patient's prescriptions changed over time, we used the following coding strategy. If the patient used two medications at any point over the study period, or changed from monotherapy to dual-therapy, they were placed in the dual-therapy category. Those that only ever used one oral agent were placed in the monotherapy category. It is notable, that it is not within the recommendations to prescribe three oral hypoglycaemic agents to manage diabetes, so we include this category with only a few values, to describe these aberrant cases. Notably, insulin-using PLWT2DM are not eligible for the programme due to cold-chain procedures and the need for monthly clinical monitoring for titration.[17]

We used the "strops" command in Stata, to identify facilities that were hospitals, and those that were primary health care (PHC) facilities (i.e. clinics or CHCs), based on the facility name. We created a variable for facility type, with two levels, namely hospital or PHC facility. We also used the "strops" function to identify neuropathy or nephropathy T2DM-related complication data and created a binomial variable, indicating if there were no recorded complication, or if there was a recorded complication (i.e. neuropathy or nephropathy). Notably diabetic retinopathy data was unavailable in either data source. As the study period was over three years, and T2DM-related

complications and facility type did not vary over time, we used the baseline category in our coding strategy.

The SEMDSA clinical care guidelines recommend three months between HbA1c tests for those sub-optimally controlled, and six months between tests for those optimally controlled.[3] We calculated adherence to the SEMDSA testing frequency guidelines for each patient by calculating the time between each HbA1c test and the test that preceded it with the Stata "datediff" command. If the preceding test was optimal, we used an interval of six months or less to define adherence and an interval of more than six months to define non-adherence. If the preceding test was sub-optimal, we used an interval of three months or less to define adherence and an interval of more than three months to define non-adherence. We then summed tests that adhered to the recommended time interval for each patient, and divided this by the number of tests per patient minus the first test (i.e. N - 1). We subtracted the first test as it did not have a test preceding it. We considered a proportion of 1 as the patients adhering to the guideline for all of their tests (e.g. if a patient had three HbA1c tests, and two adhered to the recommended time interval, then their adherence rate was 2/ (3 - 1) = 1). Thus, the adherence variable was binomial.

The CCMDD is used to distribute medication for other stable chronic conditions (e.g. hypertension (HPT), hyperlipidaemia and HIV). We used "strops" to identify the relevant conditions, to create the comorbidity variable: T2DM alone, T2DM and HIV, T2DM and dyslipidaemia, and multimorbidity (i.e. T2DM, HPT, HIV).

Data Analysis

STATA v17 was used to conduct the analysis. We used summary statistics to describe the HbA1c tests available, as well as, the frequency and proportion of those with one, two or more than three HbA1c tests performed over the study period. We also calculated the median and inter-quartile range (IQR) time interval between tests in months, median age and the median months between HbA1c test and CCMDD enrollment date. Medians and IQR were reported for all non-normally distributed continuous variables, on statistical (sktest and swilk) and graphical tests.

We summarised baseline patient characteristics (i.e. sex, age, type of facility, T2DM-related complications, type of oral hypoglycaemic therapy received and comorbidities) using frequencies and proportions for all categorical data. We summarised median HbA1c values across each

covariate's strata. Additionally, frequencies and proportions were reported by optimal and sub-optimal control across each covariate's strata. The Chi-square test was used to assess the association between glycaemic control status (optimal versus sub-optimal) and each covariate (i.e. sex, age, type of facility, T2DM-related complications, type of oral hypoglycaemic therapy received and comorbidities). A p-value less than 0.05 was considered statistically significant in the Chi-square test.

For those who had an optimal HbA1c test value at baseline, with at least one repeat test value available, we performed a survival analysis. The outcome of interest was years until sub-optimal glycaemic control. It was generated by using the date of the first sub-optimal event, in the study period. For those that remained optimally controlled to the end of the study period (i.e. those who were right censored), we used the last date of the study period (i.e. 30 June 2022). We calculated the median age (IQR), median HbA1c (IQR), median (IQR) months between HbA1c tests, median (IQR) months between the first available HbA1c test and the CCMDD enrollment date, median (IQR) number of tests per unique patient, and median (IQR) analysis time in years, by glycaemic control outcome. We summarised these patient characteristics using frequencies and proportions for sex, age, type of facility, T2DM-related complications, type of oral hypoglycaemic therapy received and comorbidities.

Univariate analysis was performed, using Kaplan-Meier curves to analyse the survival curves for the probability of maintaining optimal control by potential predictor variables (i.e. sex, age, type of facility, T2DM-related complications, type of oral hypoglycaemic therapy received and comorbidities). The log-rank test was used to compare survival curves across categorical variables' strata. We summarised frequencies, sub-optimal event frequencies and time at risk for each covariate's (i.e. sex, age, type of facility, T2DM-related complications, type of oral hypoglycaemic therapy received and comorbidities) strata. Incidence rates for developing sub-optimal control were calculated by dividing the number of sub-optimal events by the time at risk (in person-years), for each covariate's strata. Incidence rates and 95% CI were reported per 1000 person-years. We also assessed the 25^{th} percentile of survival time in years (i.e. the analysis time where 25% of subjects have become sub-optimally controlled and 75% remain optimally controlled) for each covariate strata. Variables with a p-value <0.25 were included in the multivariable Cox model. We tested interaction terms between all covariates, however none were significant.

The variables sex, facility type, type of therapy, and adherence to SEMDSA guidelines for HbA1c testing frequency were included in the final model. The assumption of proportional hazards (PH) was not upheld in the global test due to the variable facility type, consequently, an extended Cox analysis, which is used for analysis where time-varying variables exist, was conducted. We summarised the co-efficient (95% CI) and adjusted hazard ratios (95% CI) for the main model and for the time-varying coefficient model. We calculated a combined effect by adding the two models coefficients (i.e. 1- $e^{(\text{main model co-efficient+ time-varying co-efficient})}$). A confidence interval of 95% was used and a significance level of $p < 0.05$ was considered statistically significant for the Cox regression model tests.

Ethical Considerations

Ethical approval was obtained from the University of the Witwatersrand's Medical Human Research Ethics Committee (HREC no. M220232). Data access approval was obtained from the relevant custodians in the CCMDD and NHLS.

RESULTS

Participants

There were 41 145 CCMDD-enrolled patients in eThekwini, who were 18 years or older and receiving oral hypoglycaemic medication between 2018 and 2021 (**Figure 2.1**). Nineteen percent (7 960/41 145) had 1 or more HbA1c test result. Among patients with a HbA1c test available, 27% (2 147/7 960) were optimally controlled at baseline. Of these, 695 patients had 1 or more repeat HbA1c test result in the study period (**Figure 2.1**).

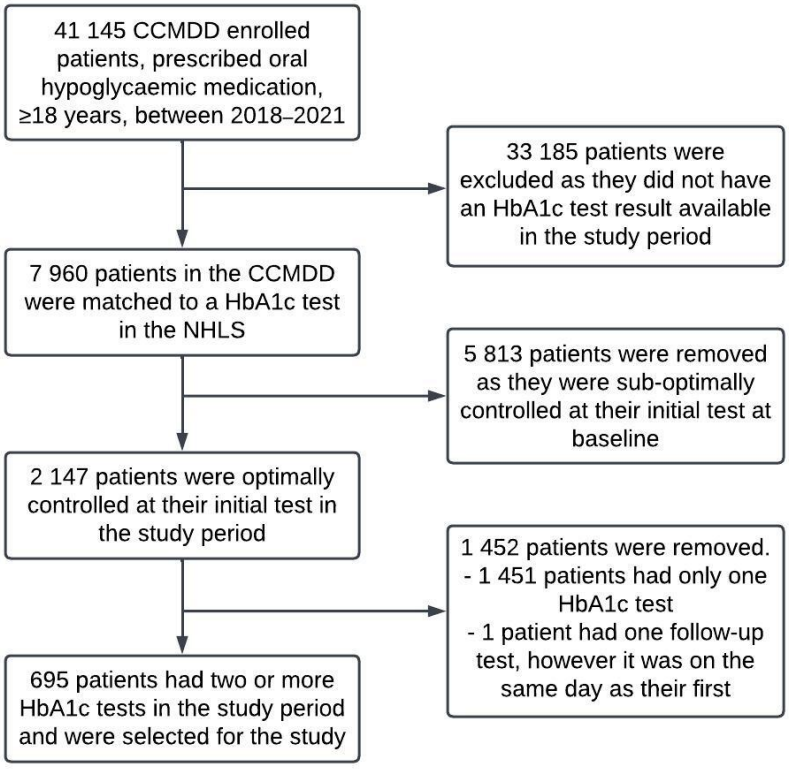

Figure 2.1*: Flow chart of study population selection. CCMDD, central chronic medication dispensing and distribution programme; HbA1c, glycated haemoglobin A1c; NHLS, national health laboratory service.*

Descriptive data

Baseline analysis results

For the 7960 CCMDD-enrolled patients, there were 12 102 HbA1c tests performed over the study period (**Table 2.1**). Of the 12 102 HbA1c test results, 66% (n=7 960) were first observations, 22% (n=2 646) were second observations and 12% (n=1 496) were the third or more observations for a unique patient. The overall median interval between tests for those with more than one test available was 12 months (IQR: 8–18). The median age of patients was 60 years (IQR: 52-67) and the median HbA1c was 8.2% (IQR: 7.0–10.0).

Demographic characteristics of the 7 960 patients with a baseline HbA1c are summarized by glycaemic control status (**Table 2.2**). Those who were excluded for being sub-optimally controlled at baseline differed from those that were included by sex, age, and type of therapy, and were similar by type of facility, T2DM-related complications, and comorbidity (**Table 2.2**).

***Table 2.1**: Description of HbA1c samples for the Central Chronic Medicines Dispensing and Distribution programme cohort receiving oral hypoglycaemic medication for T2DM, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N = 7 960).*

	Number of HbA1c tests per patient			
Characteristic	**1**	**2**	**≥3**[†]	**Total**
HbA1c samples N (%)	7 960 (65.8%)	2 646 (21.9%)	1 496 (12.4%)	12 102 (100%)
Sub-optimally controlled N (%)	5 984 (75.2%)	1 964 (74.2%)	1 181 (78.9%)	9 129 (75.4%)
Median HbA1c result (IQR)	8.1 (7.0–10.0)	8.1 (6.9–9.9)	8.4 (7.1–10.1)	8.2 (7.0- 10.0)
Median months between 1st HbA1c test & CCMDD enrolment date (IQR)	4 (-8–18)	12 (-1– 26)	18 (5–31)	7 (-6–22)
Median months between HbA1c tests (IQR)	-	12 (8–19)	9 (6–13)	12(8–18)
Median age in years (IQR)	60 (52–67)	60 (52–67)	60 (52–67)	60 (52–67)

[†]Those with 3 or more observations were grouped

***Table 2.2**: Baseline median HbA1c value by patient characteristic for the Central Chronic Medicines Dispensing and Distribution programme cohort receiving oral hypoglycaemic medication for T2DM, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021(N = 7 960).*

Characteristic	Total N=7 960 (100%) n (%)	Median HbA1c (IQR)	Sub-optimal (HbA1c >7%) N=5 813 (73%) n (%)	Optimal (HbA1c ≤7%) N=2 147 (27%) n (%)	p-value[†]
Sex					<0.001[†***]
Male	2 608 (33%)	7.9 (6.8–9.8)	1 816 (31%)	792 (37%)	
Female	5 352 (67%)(	8.2 (7.0–10.1)	3 997 (69%)	1 355 (63%)	
Median age (years)	60 (IQR:52–67)	-	59 (52–66)	62 (IQR:54–70)	<0.001[††***]
Age category (years)					<0.001[†***]
≤39 year	311 (4%)	8.5 (7.1–11)	234 (4%)	77 (4%)	
40–59 years	3 566 (45%)	8.6 (7.2–10.5)	2 759 (47%)	807 (38%)	
60–79 years	3 831 (48%)	7.8 (6.9–9.5)	2 692 (46%)	1 139 (53%)	
≥80 years	252 (3%)	7.1 (6.5–8.1)	128 (2%)	124 (6%)	
Type of facility					0.92[†]
PHC facility[a]	5 195 (65%)	8.1 (6.9–9.9)	3 792 (65%)	1 403 (65%)	
Hospital	2 765 (35%)	8.2 (7.0–10.1)	2 021 (35%)	744 (35%)	
T2DM-related complication					0.23[†]
Neuropathy or nephropathy	4 135 (52%)	8.1 (6.9–9.9)	2 996 (52%)	1 139 (53%)	
None recorded	3 825 (48%)	8.2 (7.0–10.1)	2 817 (48%)	1 008 (47%)	
Type of therapy					<0.001[†***]
Monotherapy	4 418 (56%)	7.6 (6.7–9.4)	2 870 (49%)	1 548 (72%)	
Dual-therapy	3 538 (44%)	8.8 (7.4–10.6)	2 939 (51%)	599 (28%)	
Triple-therapy	4 (0%)	9.8 (9.3–10.1)	4 (0%)	0 (0%)	
Comorbidity					0.097[†]
T2DM[b] alone	1 175 (15%)	8.4 (7.0–10.3)	880 (15%)	295 (14%)	
T2DM and HIV[c]	450 (6%)	8.6 (7.0–10.5)	335 (6%)	115 (5%)	
T2DM and HPT[d]	5 608 (70%)	8.1 (7.0–9.9)	4 094 (70%)	1 514 (71%)	
T2DM, HIV and HPT	704 (9%)	8.0 (6.8–10.1)	487 (8%)	217 (10%)	
T2DM and dyslipidaemia	23 (0%)	8.5 (6.8–10.4)	17 (0%)	6 (0%)	

[a]Primary health care, [b]Type two diabetes mellitus, [c]Human Immunodeficiency Virus, [d]Hypertension; [†]p-value for the chi-square test for sub-optimal vs optimal; [††]p-value for the Kruskal –Wallis test for median age by sub-optimal vs optimal; Significance level (p-value): [*]p<0.05, [**]p<0.01, [***]p<0.001.

Survival analysis results

Among the 695 study participants who had an optimal baseline HbA1c test result, and with one or more repeat HbA1c test result (**Table 2.3**), the median age was 61 years (IQR: 53–69). The overall median interval between HbA1c tests was 13 months (95% CI: 10–19) and was similar for those optimally (12 months; 95% CI: 10–19) and sub-optimally controlled (13; 95% CI: 10–20) (**Table 2.3**). The median time between the first HbA1c test and the patient's CCMDD enrolment date was three months before enrolment (95% CI: 13 months prior–10 months post) (**Table 2.3**). The median number of HbA1c tests per patient was 2 (IQR: 2–2), with 2 as a minimum and 13 as a maximum. The median time in the study was 4.7 years for those who remained optimally controlled and was 3.2 years for those who became sub-optimally controlled (**Table 2.3**). Of the 695 patients, 23 HbA1c tests were in the period of the level 4-5 COVID-19 lockdown in South Africa (i.e. 27th March 2020–1 June 2020). The median time between test during the lockdown period was 11.8 (95% CI: 6.4–14.9) months versus 12.1(95% CI: 8.9–20.1) months in lesser level, or non-lockdown periods.

Table 2.3*: Descriptive characteristics of the T2DM CCMDD-enrolled participants with ≥1 repeat HbA1c test value available eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N =695).*

Characteristic	Total (N=695)	Sub-optimal event (N=242)	Remained Optimal (N=453)
Median Age (IQR)	61 (53– 69)	59 (51–68)	61 (54–69)
Median HbA1c (%)	6.7 (6.1–7.3)	7.5 (7.2– 8.6)	6.3 (6.0–6.6)
Median months between HbA1c tests (IQR)	13 (10–19)	13 (10–20)	12 (10–19)
Median months between CCMDD enrolment date and baseline HbA1c test date (IQR)	-3 (-13–10)	-4 (-15–6)	-2 (-13–11)
Median number HbA1c tests (IQR; min-max)	2 (2–2; 2–13)	2 (2–2; 2–6)	2 (2–2; 2–13)
Median analysis time in years (IQR; min-max)	4.7(3.8– 4.7; 0.4–4.7)	3.2(2.0–3.9; 0.4–4.7)	4.7(4.7–4.7; 4.7–4.7)

Additionally, the majority attended primary healthcare facilities (71%; 496/695) and were prescribed monotherapy (70%; 484/695) (**Table 2.4**). The most common comorbidity was hypertension (71%; 490/695), and 54% of the participants (377/695) having a T2DM-related complication of neuropathy or nephropathy (**Table 2.4**).

Univariate Results

Demographic Information

The incidence rate for developing sub-optimal control over time was higher for male patients (155.04 per 1000 person-years) than for female patients (127.17 per 1000 person-years), however, it was not significant ($p=0.12$) (**Table 2.4 and Figure 2.2**). Age was also not significantly associated with developing sub-optimal glycaemic control ($p=0.32$), with higher incidence rates for younger age groups (146.11 and 152.60 per 1000 person-years among those aged ≤39 years and those aged 40–59 years,

respectively); and lower incidence rates for those aged 60-79 years (128.22 per 1000 person-years) and those aged ≥80 years (88.58 per 1000 per years) (**Table 2.4 and Figure 2.2**).

Diabetes Severity

Patients attending PHC facilities had a significantly higher incidence rate of developing sub-optimal control (152.53 per 1000 person-years), compared to those attending hospital facilities (105.35 per 1000 person-years; p=0.03) (**Table 2.4 and Figure 2.2**). Compared to patients with no reported diabetes-related complications, patients with nephropathy and neuropathy had a lower incidence of sub-optimal control (128.95 versus 146.38 per 1000 person-years; p=0.35) (**Table 2.4 and Figure 2.2**). Patients on dual-therapy had a significantly higher incidence of sub-optimal glycaemic control, at 184.33 per 1000 person-years, compared to those who only used one oral medication at 118.15 per 1000 person-years (p=0.00) (**Table 2.4 and Figure 2.2**).

Quality of Care

The incidence rate of sub-optimal glycaemic control was significantly higher for those who did not have a follow-up HbA1c test within SEMDSA-recommended guidelines (i.e. within three months for those sub-optimally controlled and within six monthly for those optimally controlled) (143.98 per 1000 person-years) compared to those who did have a follow-up test within the SEMDSA-recommended time frame (59.86 per 1000 person-years, p=0.01) (**Table 2.4 and Figure 2.2**). Those enrolled in the CCMDD between 7–12 months had lower incidence rates of sub-optimal control than those enrolled for <7 or >12 months, however, this was not a significant finding (p=0.75).

Comorbidities

Patients with T2DM alone and with HPT comorbidity had lower incidence rates (128.50 and 133.66 per 1000 person-years, respectively), than those with multimorbidity (i.e., T2DM, HPT, and HIV), and those with HIV comorbidity (155.91 and 157.86 per 1000 person-years, respectively). However, these results were not statistically significant (p=0.83) (**Table 2.4 and Figure 2.2**).

Table 2.4 *Univariate survival analysis (Kaplan-Meier and log-rank test values) across potential predictor's strata for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N=695).*

Characteristic	Number of cases	Number of sub-optimal events	Time at risk (years)	Incidence rate of sub-optimal glycaemic control per 1000 person-years (95% CI)	25th percentile of survival time (years)†	p-value
Sex						0.1217§
Male	248	95	612.73	155.04 (126.80–189.58)	2.61	
Female	447	147	1 155.89	127.17 (108.19–149.49)	3.16	
Age						0.3238
17–39 years	24	10	68.44	146.11 (78.61–271.55)	3.62	
40–59 years	298	113	740.70	152.60 (126.87–183.45)	2.69	
60–79 years	333	110	857.87	128.22 (106.37–154.57)	2.86	
≥80 years	40	9	101.60	88.58 (46.09–170.25)	3.53	
Type of facility						0.0257*§
PHC facility[a]	496	180	1180.09	152.53 (131.80–176.52)	2.91	
Hospital	199	62	588.52	105.35 (82.13–135.12)	3.03	
T2DM-related complication						0.3447
Nephropathy or neuropathy	377	125	969.34	128.95 (108.22–153.66)	2.71	
None recorded	318	117	799.27	146.38 (122.12–175.46)	3.18	
Type of therapy						0.0006**§
Monotherapy	484	150	1269.52	118.15 (100.68–138.66)	3.41	
Dual-therapy	211	92	499.10	184.33 (150.27–226.12	2.12	
Comorbidity						0.8315
T2DM[b] alone	86	28	217.91	128.50 (88.72–186.10)	3.18	
T2DM and HIV[c]	39	16	101.36	157.86 (96.71–257.67)	1.92	
T2DM and HPT[d]	490	168	1256.94	133.66 (114.90–155.48)	2.88	
T2DM, HIV and HPT	80	30	192.41	155.91 (109.01–222.99)	3.34	
Months enrolled in CCMDD						0.7485
≤6 months	230	79	609.44	129.63 (103.98–161.61)	2.74	
7–12 months	69	23	180.80	127.21 (84.54–191.43)	3.60	
≥13 months	388	138	957.67	144.10 (121.96–170.26)	2.71	
HbA1c testing frequency adheres to SEMDSA guideline‡						0.0064**§
Yes	63	9	150.34	59.86 (31.15–115.05)	4.44	
No	632	233	1 618.28	143.98 (126.63–163.71)	2.86	
Total	**695**	**242**	**1768.62**	**136.83**	**2.88**	

[a]Primary health care, [b]Type two diabetes mellitus, [c]Human Immunodeficiency Virus, [d]Hypertension; [e]Central Chronic Medicines Dispensing and Distribution; †The analysis time where 25% of subjects have become sub-optimally controlled and 75% remain optimally controlled. ‡SEMDSA clinical care guidelines recommend three months between HbA1c tests for those sub-optimally controlled, and six months between tests for those optimally controlled; Significance level (p-value): *p<0.05, **p< 0.01, ***p<0.001; § Log-rank test of equality across strata, with p-values below 0.25 for the predictors, will be included as potential candidates for the final Cox model.

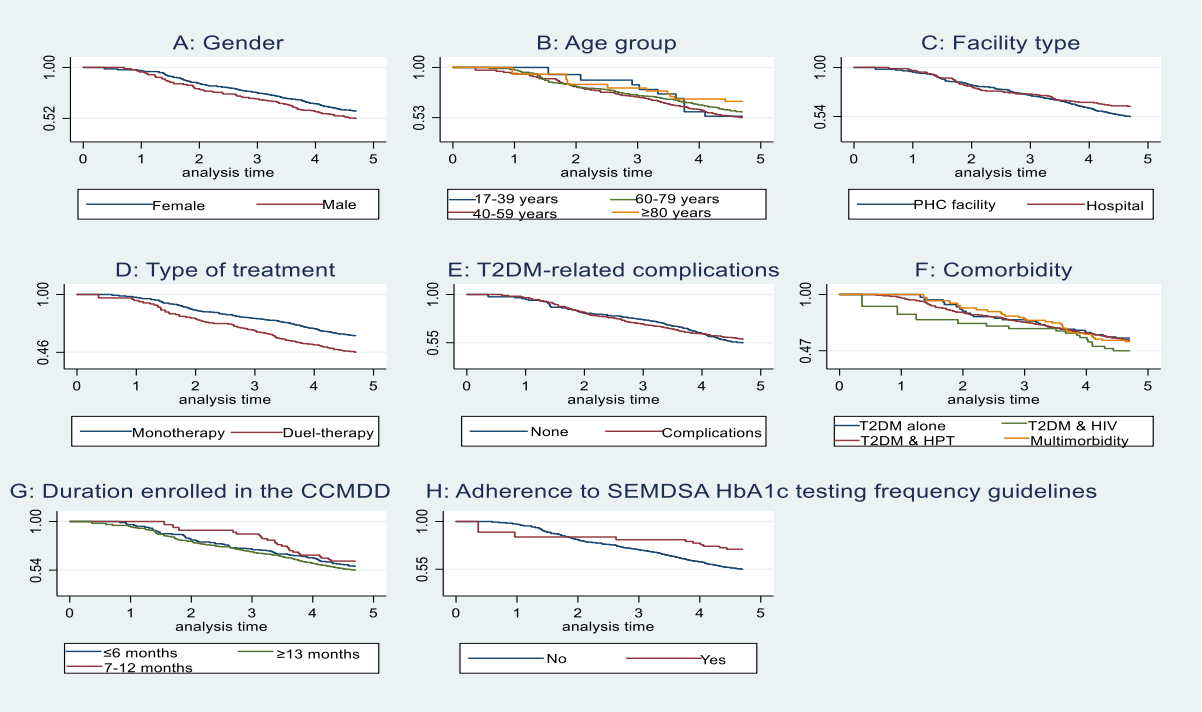

***Figure 2.2**: Kaplan-Meier survival curves for the probability of maintaining optimal glycaemic control, by potential predictors, for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N=695).*

Multivariable Regression Results

Predictors from the Log-rank test of equality, with p-values below 0.25, were sex, facility type, type of therapy, and adherence to SEMDSA guidelines for HbA1c testing frequency, and were included in the final model.

Demographic Information

When holding other variables constant, male patients had a 21 times higher hazard than female patients for developing suboptimal control over the study period (p=0.14) (**Table 2.5**).

Diabetes Severity

The adjusted hazard for those attending hospitals, in the main effects model, was 45% higher than those attending PHCs (p=0.26). However, on treating facility type as a time-varying covariate, by interacting its effect with the natural log of time, this hazard decreases by 50% for each unit increase in the natural log of time (p=0.03). Thus, the combined effect is that of a 27% reduction in risk of developing sub-optimal control for those attending hospitals compared to those attending PHC facilities over the study period. The adjusted hazard for those using dual-therapy was 50 times higher than the hazard among those using monotherapy (p=0.00) (**Table 2.5**).

Quality of Care

Patients who had their HbA1c tests according to the SEMDSA-recommended guidelines (i.e. within three months for those sub-optimally controlled and within six monthly for those optimally controlled) had an adjusted hazard 54% lower than the hazard for those whose HbA1c test did not adhere to the SEMDSA guidelines (p=0.02) (**Table 2.5**).

***Table 2.5**: Multivariable Cox regression model for factors associated with developing sub-optimal glycaemic control for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021(N=695).*

Characteristic	Co-efficient (95% CI)	Adjusted Hazard ratio (95% CI)	p-value
Main model			
Sex			
Male	0.194 (-0.064–0.453)	1.214 (0.938–1.572)	0.141
Female	1	1	
Facility type			
PHC	1	1	
Hospital	0.372 (-0.276–1.020)	1.450 (0.759–2.771)	0.261
Type of therapy			
Monotherapy	1	1	
Dual-therapy	0.407 (0.147–0.668)	1.503 (1.158–1.950)	0.002**
HbA1c testing frequency adheres to SEMDSA guideline†			
Yes	-0.770 (-1.441– -0.100)	0.463 (0.237–0.905)	0.024*
No	1	1	
Time-varying coefficient model			
Facility type x ln(t)			
PHC	1	1	
Hospital	-0.690 (-1.313– -0.065)	0.502 (0.269–0.937)	0.031*

†SEMDSA clinical care guidelines recommend three months between HbA1c tests for those sub-optimally controlled, and six months between tests for those optimally controlled; Significance level (p-value): *p<0.05, **p<0.01, ***p<0.001.

DISCUSSION

In this study, we aimed to determine the proportions of T2DM CCMDD-enrolled patients achieving optimal glycaemic control and factors associated with an increased hazard for developing sub-optimal control. We found that only 27% of CCMDD-enrolled patients in eThekwini had optimal glycaemic control at their first HbA1c test in the study period; and that those receiving dual therapy had an increased risk, while those who adhered to HbA1c testing frequency guidelines had a lower risk. Those attending hospitals initially had a higher hazard, however this effect decreased over time, resulting in a combined lower hazard compared to those attending PHC facilities.

Our finding of 27% of CCMDD-enrolled patients in eThekwini, having optimal control at their baseline HbA1c test result, was similar to findings from a cross-sectional file audit at Tshwane PHC facilities, conducted in 2019, that revealed that only 29% of CCMDD-enrolled

patients had optimal glycaemic control.[18] While our finding is congruent with this past study, we expected more patients to be optimally controlled at their HbA1c reading closest to CCMDD enrolment; as patients need to have achieved a stable condition (based on two consecutive normal FPG tests) to qualify for enrolment.[12]

A reason for this discrepancy could be our study's use of HbA1c to define glycaemic control versus the use of FPG by the CCMDD. We used HbA1c based on the IDF recommending HbA1c as the gold standard for monitoring glycaemic control.[2] However, past studies have found HbA1c and FPG to be incongruent.[7] The use of FPG, by the CCMDD, may be creating a false stable target group.

An additional reason may be the time interval between the first available HbA1c test and the patient's CCMDD enrolment date. The median interval was three months, making it valid, as a baseline measure. However, there was wide variation in the timing of the HbA1c test relative to the CCMDD enrolment date (95% CI: 13 months prior−10 months' post). Nevertheless, our finding is concerning and highlights an unmet need in the care cascade, that must be addressed to meet targets set out in SA's NSP (i.e. 50% of those receiving treatment achieving glycaemic control by 2030).[9]

We also found that adherence to the SEMDSA guidelines for HbA1c testing frequency was poor in this cohort. Firstly, over the three-year study period, 81% of T2DM patients had no HbA1c tests performed. Secondly, when looking at those optimally controlled at their first reading, 32% (695/2 147) of patients had a repeat test/s performed in the study period. This finding, is in agreement with a study of NHLS HbA1c data, from GP (2015−2018), where 21% of patients with a first-ever HbA1c test in the NHLS, who were optimally controlled, had a follow-up result/s over their four-year study period.[19] These results are concerning as the STG for T2DM recommends that patients receive a HbA1c test annually, or 6 monthly when changes are made to medications prescribed. It is worth noting, that 33% (230/695) of the cohort, were enrolled in the CCMDD for ≤6 months. However, due to the 6-month window we included for HbA1c tests performed on either side of the study period, it is unlikely that many repeat tests were missed.

Thirdly, for those with repeat tests, the median interval between tests was 12 months for those that were optimally controlled and 13 months for those who were sub-optimally controlled. This is not aligned with the SEMDSA guidelines of 6 months for those optimally

controlled, and 3 months for those sub-optimally controlled.[3] It is noteworthy that the CCMDD changed its activities during the COVID-19 pandemic, so that prescription collections were extended from two-monthly to three-monthly, and clinic visits were extended from six-monthly to annually.[20] We hypothesized that the resultant extended time between clinical check-ups may have contributed to the longer interval between HbA1c tests over this lockdown period, however our results revealed similar time intervals between tests in periods of higher (i.e. level 4-5) lockdowns and periods with lower levels of lock down (i.e. levels 0-3).

Lastly, adherence to SEMDSA guidelines was significantly protective against developing sub-optimal control in those who began optimally controlled (aHR = 0.463, 95% CI: 0.237–0.905, p-value = 0.024). Correspondingly, adherence to HbA1c testing guidelines for T2DM patients has been demonstrated internationally. An Australian study, monitoring longitudinal HbA1c values in T2DM patients visiting a general practitioner (2013–2018), found that adherence to the Australian guidelines for HbA1c testing intervals, which are in line with the SEMDSA guidelines, resulted in patients remaining controlled over time. While low adherence to guidelines resulted in increased HbA1c readings, sub-optimal glycaemic control, and higher risk for chronic kidney disease.[21] Similarly, a United Kingdom (UK) study compared glycaemic control in patients receiving three-monthly testing to those receiving annual testing, using data from clinical laboratories, and determined that three-monthly testing was associated with a 3.8% reduction in HbA1c versus annual testing that resulted in a 1.5% increase in HbA1c.[22]

This finding demonstrates that despite the policies for care being in place, the recommended policy is not being sufficiently implemented within the CCMDD cohort. While bi-annual clinical follow-ups are appropriate and fall within SEMDSA guidelines, for those who are optimally controlled, it is not appropriate for those who are sub-optimally controlled. These patients require intensification of their clinical visits and HbA1c testing to at least as frequently as every three months. As it stands, many opportunities to intervene, educate and improve glycaemic control and T2DM-related health outcomes for PLWT2DM in eThekwini, are being missed.

We also found that patients who were prescribed dual-therapy were more vulnerable to developing sub-optimal control. This concurs with results obtained in a study on the determinants of glycaemic control for PLWT2DM in Lebanon, where those using dual-

therapy compared to monotherapy, had twice the odds of being uncontrolled (OR 2.35, 95% CI 1.58–3.50).[23] This result could be attributed to dual-therapy being used only for patients who failed to attain optimal glycaemic control with metformin alone. As such, this group may reflect individuals with higher rates of past failures or vulnerabilities to achieving glycaemic control, before obtaining a stable status for CCMDD enrolment.

Moreover, we found an increased rate of developing sub-optimal control over time, for those attending PHC facilities compared to those attending hospitals. This result agrees with a study of NHLS HbA1c data, from GP, between 2015 and 2018, where those with sub-optimal glycaemic control, who attended hospitals had a higher likelihood of achieving optimal control, than those attending PHC facilities.[19] This may be explained by reports from PHC facilities of under-resourcing,[24–27] lack of equipment,[27] lack of infrastructure,[26,27] and poor willingness of healthcare providers to adapt and integrate diabetes care into their service provision.[26]

Recommendations:

To address the high proportion of sub-optimally controlled patients enrolled in the CCMDD, we recommend that the CCMDD consider amending their enrolment criterion to two consecutive HbA1c tests, rather than FPG tests. Additionally, including a self-efficacy score as an additional enrolment criterion may improve survival rates, especially among those receiving dual-therapy to manage their conditions. These recommendations agree with recommendations made by Ngassa Piotie et. al. (2019) following their Tshwane PHC facilities file audit of CCMDD-enrolled patients.[18] Future studies may also consider comparing glycaemic control for a CCMDD cohort using both FPG and HbA1c test results.

We also recommend that a feedback loop needs to exist, between the CCMDD and either the NHLS or the patient's clinical results at facility-level, so they can monitor the enrolled patient's HbA1c. In this way, patients who change state from optimal to sub-optimal can be flagged to exit the programme. This is critical in the context of diabetes, which is a progressive disease by nature. As the disease progresses, medication management (i.e. adding insulin to the regime) and the prevention/management of T2DM-related comorbidities must be escalated accordingly. If there is no feedback of glycaemic control status to the programme, clinical and patient inertia may well be compounded for enrolled patients that become sub-optimally controlled.

Additionally, in South Africa's resource-constrained public health sector, we recommend that the programme consider more frequent HbA1c monitoring of their patients using community health workers,[28–30] T2DM education/support groups within communities,[31] or mobile health (mHealth) technology (e.g. for patients waiting in CCMDD ques) and innovations to support self-management.[32] In fact, our results suggest that CCMDD-enrolled patients may be better managed if point of care (PoC) testing (i.e. HbA1c or FPG) and management is built into the programme at the pick-up points, rather than at already over-burdened facilities. Such community-based interventions would offload already overburdened PHC facilities. These approaches are aligned with existing policies in South Africa, such as the Primary Health Care Re-engineering policy and Integrated Chronic Disease Management approach. These policies seek to mobilise, build on existing skills, and extend the scope of practice for community health workers, historically used for HIV/AIDS home-based management, to deliver NCD services, such as screening and patient-education.[28,33] Local and international reports indicate that savings incurred from treating T2DM complications would offset costs to implement such programmes[34–36]; however, this would require a detailed cost-benefit analysis of each recommended approach.

Furthermore, healthcare workers should be trained in the guidelines for care for PLWT2DM, with an emphasis on the critical nature of achieving stable, optimal glycaemic control for this population. Previous studies have revealed that knowledge of the SEMDSA and STG guidelines among healthcare workers in PHC facilities is poor.[24]

Additionally, to determine why so few HbA1c tests were performed for the CCMDD cohort, over the study period, facility-based audits and further qualitative studies are needed to establish if barriers to care exist for HbA1c testing at eThekwini hospitals and PHC facilities, alike. Additionally, future studies should consider matching HbA1c results using more advanced probabilistic matching techniques. As the CCMDD does not dispense insulin, the insulin-using PLWT2DM population in eThekwini are not represented in this study. We would recommend further studies to determine the unmet need in the cascades of care for important portion of the population of PLWT2DM.

Study limitations and strengths

There were some limitations to consider in this study. There were limited HbA1c test results available in the CDW for the study time period, thus the survival analysis results may need to

be interpreted with caution. Also, information on factors known to be associated with sub-optimal control in PLWT2DM was not available in either dataset. As a result, race, other comorbid conditions (i.e. tuberculosis), obesity measures (weight, height, BMI), lifestyle factors (i.e. smoking, alcohol use, diet, physical activity indices), self-efficacy and socioeconomic factors were not included. Notably, as diabetes is a progressive condition, duration of diabetes (rather than age) is an important predictor for sub-optimal control, and the development of T2DM-related complications, however, it was not available in either data source. These unavailable variables may represent unaccounted for confounding or modifying effects, which may have distorted our results.

Despite these limitations, our study's strengths were using retrospective data from T2DM patients spread across 13 hospitals and 107 PHC facilities in eThekwini, thus suggesting a good representation of the general CCMDD-enrolled population in eThekwini. This was also the first study of CCMDD-enrolled patients in eThekwini. Despite the CCMDD being a large public health programme, this was the first time CCMDD-enrolled patients were linked to their clinical HbA1c results, to monitor and evaluate glycaemic control over time.

CONCLUSIONS

While the CCMDD is invaluable in improving access to medication for PLWT2DM, this study, can alert policy-makers, within the NDoH and CCMDD, that significant barriers to care still exist, as the majority of CCMDD patients are not achieving optimal glycaemic control. Addressing pertinent issues, such as reassessing enrolment criteria and creating exit criteria for those who become sub-optimally controlled, are critical. In order to flag sub-optimal cases, a mechanism needs to be established for the frequent feedback of HbA1c values into the CCMDD. Furthermore, in South Africa's resource-constrained public health environment, innovative technology and community-based interventions are needed to increase HbA1c testing frequency, to align to SEMDSA guidelines, for this cohort.

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Disclaimer: The views expressed in the submitted article are my own and not an official position of the institution or funder.

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CHAPTER 3 – EXTENDED METHODS

3.1 INTRODUCTION

This chapter will describe the approaches used to determine sub-optimal glycaemic control over time, among T2DM patients enrolled in a chronic medication dispensing and distribution programme, from 2018 to 2021. The study setting, the district of eThekwini in KZN, is described. The study participants (i.e. all patients captured in the eThekwini CCMDD) and eligibility criteria for the descriptive and survival analyses components are discussed. The CCMDD and NHLS data sources are described, as are the variables that we extracted from each data set. Data management and analysis will be discussed in detail. Lastly, ethical guidelines followed and ethical issues will be considered.

3.2 STUDY DESIGN

We conducted a retrospective cohort study using secondary data from CCMDD and NHLS data sources.

3.3 STUDY SETTING

The study took place in the district of eThekwini in KZN, South Africa. **Figure 3.1** shows eThekwini's geographical location within KZN. In 2019, eThekwini had a population of 3 987 648 and accounted for 34.7% of the KZN population (59). In terms of the demographic composition, 51% of the population is female and 55% of the population are of working age (between 20–59 years of age), with 8% of the population being over 60 years of age (59). Furthermore, in terms of ethnicity, 74% of the population are Black Africans, 18% are Indian, 6% are White and 2% are Coloured (59). eThekwini contains eight community health clinics (CHCs), 106 clinics, three district hospitals, one tertiary hospital, four specialized hospitals, and five regional hospitals (59). There are 220 approved external chronic medication PuPs located within the eThekwini community (59).

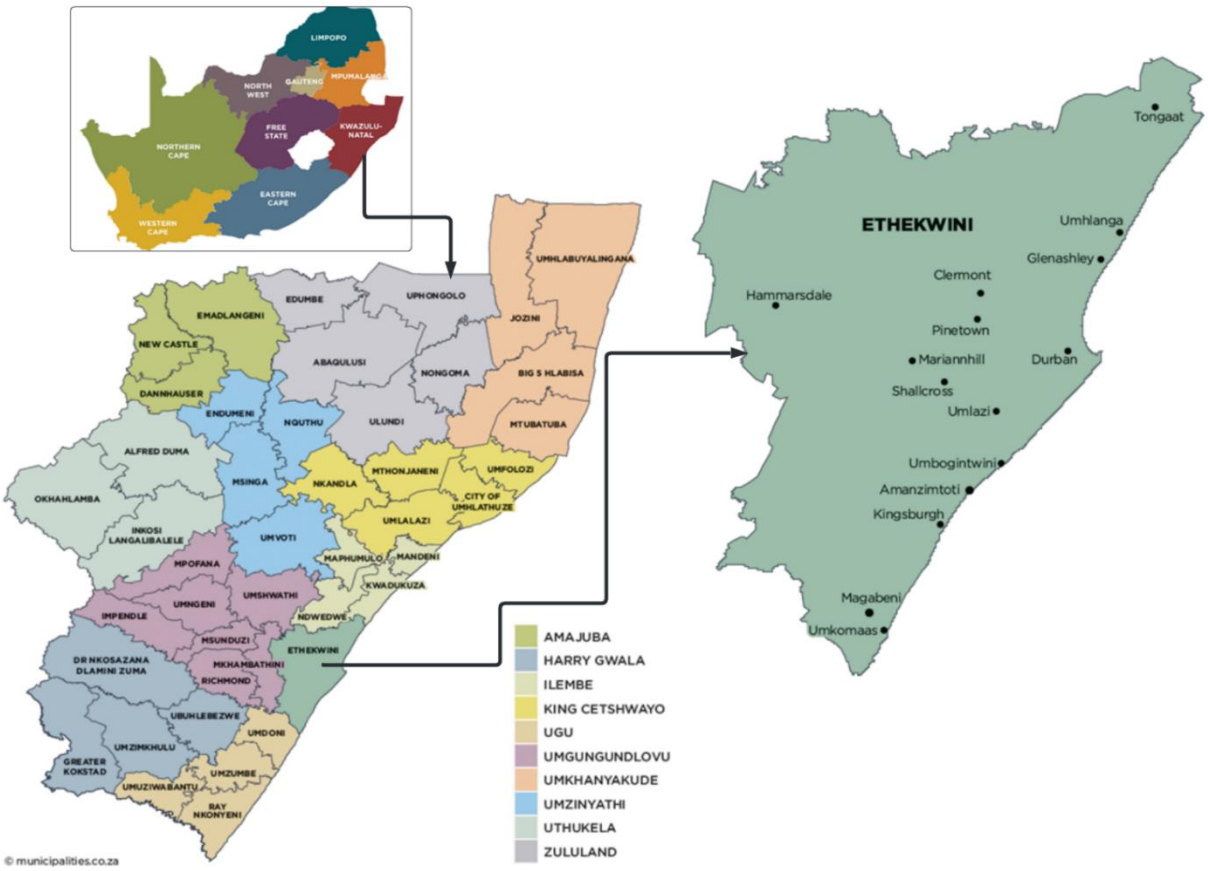

Figure 3.1*: Map of South African Provinces, KwaZulu-Natal districts and the eThekwini sub-districts* (60)

3.4 PARTICIPANTS

The study population included all T2DM adult patients (male and female) aged over 18 years enrolled in the eThekwini CCMDD database, between 19th April 2018 and 30th December 2021 (**Figure 3.2**).

3.4.1 Eligibility Criteria

As this was a retrospective study, involving longitudinal data collected from the CCMDD, and NHLS CDW laboratory data, no sampling was performed for this analysis. The following eligibility criteria were used:

- T2DM patients aged more than 18 years, enrolled in the CCMDD and receiving oral hypoglycaemic medication, in eThekwini, KZN province between 19th April 2018 and 30th December 2021.

- At least one HbA1c test recorded in CDW between 19th October 2017 and 30th June 2022 (i.e. a six-month window on either side of the CCMDD enrolment date range).

3.4.2 Exclusion criteria

- Patients in the CCMDD extract who were not receiving oral hypoglycaemic medication were excluded (**Figure 3.2**).
- For objective 1 patients without any HbA1c tests available in the study period were excluded (**Figure 3.2**).
- For objective two and three, all those without follow-up HbA1c tests were excluded (**Figure 3.2**).
- For the survival analysis in objective four, all those not optimally controlled at the HbA1c measure closest to CCMDD enrolment date, were excluded. Furthermore, all those without follow-up HbA1c tests were excluded (**Figure 3.2**).

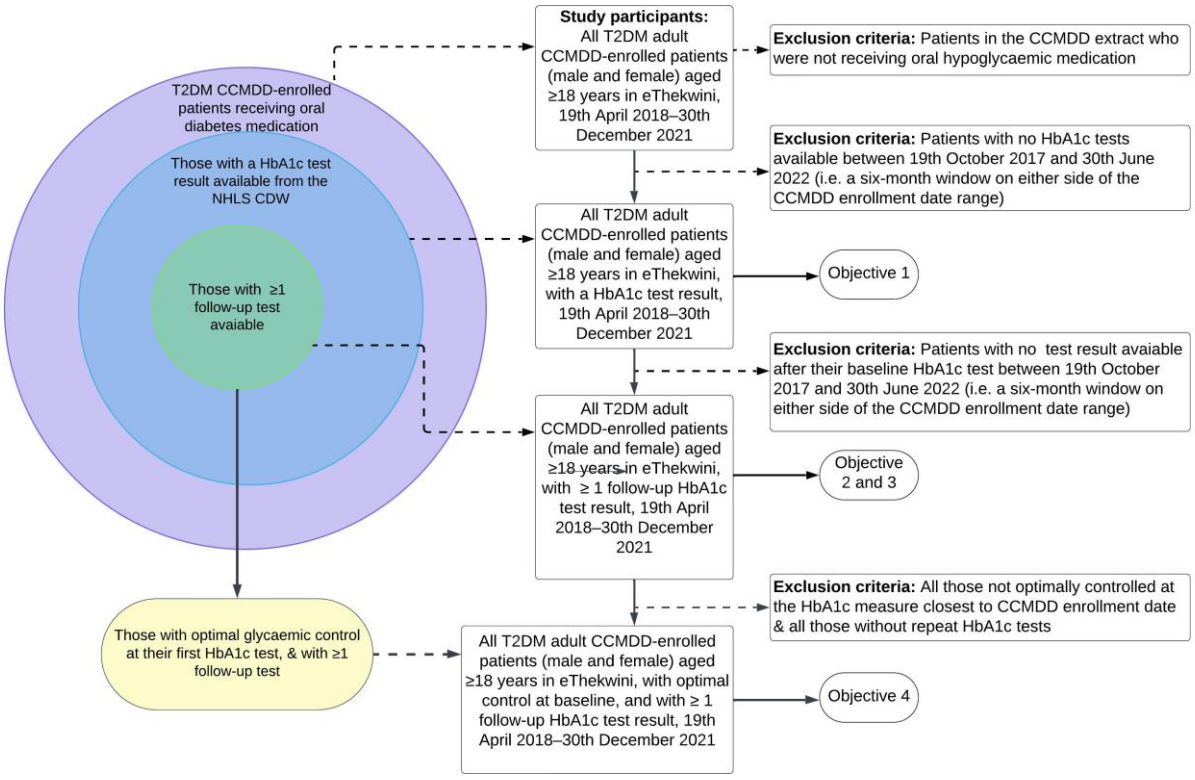

***Figure 3.2**: Study participants and selection criteria per objective for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, South Africa*

3.5 DATA SOURCES

The CCMDD dataset contains demographic information on T2DM patients that have a stable condition (FPG <7mmol/L for 2 consecutive readings) for the eThekwini cohort between 2018–2021. However, glycaemic control (HbA1c), cholesterol measures (i.e. LDL) and the time interval between HbA1c measures are not recorded. The NHLS serves all nine provinces of South Africa and provides laboratory services to 80% of the population served under the public health system at the national and provincial levels (61). NHLS is the sole provider of HbA1c tests in the South African Public sector. The results of all glycaemic control tests ordered through the network of laboratories are electronically fed to and housed in the CDW. Data for the present study in eThekwini, was obtained from NHLS for the period from 18th October 2017–30th June 2022. It was used to supplement CCMDD information for HbA1c clinical measures, by merging the datasets.

3.6 DATA MANAGEMENT AND VARIABLES

Data was provided by the CCMDD as an Excel spreadsheet and exported to STATA version 17 for cleaning and analysis. The data was checked for errors, inconsistencies, outliers, and missing data. Any duplicate participants and duplicate observations per participant, were identified and removed.

3.6.1 Merging variables

We extracted demographic information (name, ID, or file number identifier), to allow for the merging of data, for T2DM patients enrolled in the CCMDD in eThekwini. The data was sent to a key person within NHLS, to retrieve all HbA1c and LDL tests for each patient in the CCMDD cohort from 2017. We allowed a six-month window, for the HbA1c reading from the clinical visit preceding the patient's first encounter with the CCMDD, to be included. Once extracted by NHLS data managers, the primary investigator cleaned both datasets, reshaped the CCMDD data to a wide format, and merged each patient in the CCMDD data set to their HbA1c results, using a unique patient ID (**Appendix 10**). The data was then de-identified. The variables for HbA1c test date, the HbA1c result, and the unique patient ID, were used to determine a duplicate observation. Data variables were unstrung and formatted as numerical, date values or encode as categorical variables, as was appropriate.

3.6.2 Glycaemic Control

We used the continuous HbA1c value for descriptive analysis. We also used it to create a binary variable for optimal and sub-optimal control, for the outcome variable of the survival analysis. This study defined glycaemic control as optimal if the HbA1c reading was 7% or less and as sub-optimal for values above 7%. This is per the 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines and the 2020 South African Standard Treatment Guidelines (STG) (4,16,17). Both recommend using HbA1c as a monitoring tool as it captures glycaemic control over two to three months (4,16,17).

For those CCMDD-enrolled patients with an available HbA1c test result, the baseline HbA1c was the first recorded reading within the study period. For those CCMDD-enrolled patients with a follow-up HbA1c test result available, both the first and the last recorded readings were used. For the survival analysis, only those optimally controlled at their first reading in the study period were used, and time-to-failure was calculated for the first change of status to sub-optimal control.

We also created a categorical variable from the HbA1c value, where values less than or equal to 7% were optimal, and sub-optimal values were further sub-catagorised as 7.1–8.9% (poor but acceptable), 9–11.9% (very poor- at higher risk for T2DM-related complications and need to reassess management), and 12% or more (very poor and at an even greater risk for T2DM-related complications).

3.6.3 Demographic Information

We created recoded a sex variable using the sex variable from the CCMDD dataset. Age was calculated, using the "datediff" command in Stata. As age was time-varying for each HbA1c test, we subtracted the HbA1c sample collection date for the relevant test (sourced from the NHLS data), from the patient's date of birth (sourced from the CCMDD data) for each HbA1c test result entry in the line list by unique ID. Once calculated, we catagorised age in years, in four levels, as follows: 18–39, 40–59, 60–79 and 80 or over. We used these categories as the age data was skewed and we suspected nonlinearity. We included the categories 18–39 and 80 or over, despite the relatively fewer values to isolate the aberrant values in these categories.

3.6.4 Intermediate targets for cardiac health

The SEMDSA guidelines include measures for cardiovascular risk factors, such as dyslipidemia, as T2DM is an additional risk factor for macrovascular complications causing coronary artery disease (CAD) (4). Clinical data for LDL cholesterol was used as a measure for dyslipidemia (4). We recoded LDL as optimally controlled if it was less than 1.8mmol/L or sub-optimally controlled if it was greater than or equal to 1.8mmol/L. We extracted LDL measures from the NHLS merge, however, there were only five measures in total extracted from the NHLS, and as such, we dropped this component from the analysis.

3.6.5 Diabetes severity

Data on the type of treatment, facility type and diabetes-related complications were extracted. Information on medications used to achieve glycaemic control was extracted from the CCMDD data. Metformin is initially used alone. Dual oral therapy is when a second medication (e.g., sulphonylurea) is added for those not achieving targets on monotherapy (1,4,16). Notably, patients taking insulin, with more progressive disease, were not included in the CCMDD programme, due to cold-chain procedures and insulin-users requiring monthly clinical review for titration (62). Since the patient's prescriptions for oral hypoglycaemic medications changed over time, we used the following coding strategy. If the patient used two oral hypoglycaemic medications (dual-therapy) at any point over the study period, or changed from monotherapy (i.e. one oral hypoglycaemic medication) to dual-therapy, they were placed in the dual-therapy category. Those that only ever used one oral hypoglycaemic agent were placed in the monotherapy category. While not within the recommendations, some patients were receiving three oral hypoglycaemic agents to manage their diabetes in a script. These patients were catagorised as triple-therapy.

The facility name was extracted from the CCMDD data. We used the “strops” command in Stata, to identify facilities that were hospitals, and those that were PHC facilities (i.e. clinics or CHCs), based on the facility name. We created a binomial variable for facility type, with two levels, namely hospital or PHC facility. We assumed more complex cases were managed at hospital-level, and that less complex cases would be managed at PHC-level.

T2DM-related complications, in terms of the development of diabetic neuropathy or nephropathy, were extracted, from the CCMDD data. We created a binomial variable, indicating if there were no recorded complication, or if there was a recorded complication (i.e. neuropathy or nephropathy). We assumed that T2DM-related complications were linked to poorer glycaemic control. As the study period was over three years, and T2DM-related complications and facility type did not vary over time, we used the baseline category in our coding strategy.

3.6.6 Quality of Care

We measured the quality of care by extracting the median interval between HbA1c tests, as well as the median duration of enrolment in the CCMDD programme. For those with stable glycaemic levels, HbA1c is recommended to be monitored six monthly (SEMDSA guideline) or annually (STG/EML guideline) (4,16,17). For those who are not in the target range or who have had a change in their T2DM management, monitoring is recommended three to six-monthly in the STG and three-monthly in the SEMDSA (4,16,17). As those enrolled in CCMDD only attend the clinic bi-annually, rather than monthly, we were interested to see if these guidelines for care were being adhered to. As such, we calculated adherence to the guidelines for each patient by calculating the time between each HbA1c test and the test that preceded it with the Stata "datediff" command. If the preceding test was optimal, we used an interval of six months or less to define adherence and an interval of more than six months to define non-adherence. If the preceding test was sub-optimal, we used an interval of three months or less to define adherence and an interval of more than three months to define non-adherence. We then summed tests that adhered to the recommended time interval for each patient, and divided this by the number of tests per patient minus the first test (i.e. N - 1). We subtracted the first test as it did not have a test preceding it. We considered a proportion of 1 as the patients adhering to the guideline for all of their tests (e.g. if a patient had three HbA1c tests, and two adhered to the recommended time interval, then their adherence rate was 2/ (3 - 1) = 1). Thus, the adherence variable was binomial.

Furthermore, the "datediff" command was also used to determine the time each patient was enrolled in the programme. We used data extracted from the CCMDD to subtract the first prescription date from the last prescription date in the study period. This was then used, to create a categorical variable.

3.6.7 Comorbidities

We extracted the first and last medication prescriptions for each patient from the CCMDD. As medications used to treat T2DM, HPT, hyperlipidaemia and HIV are condition-specific, we used them to create the comorbidity variable. Comorbidity included T2DM alone, T2DM with HIV, T2DM with HPT, or multimorbidity (T2DM with both HIV and HPT). Comorbidities did not vary much over the course of the study, due to the short study period, so we used a coding strategy where if a patient had the comorbidity at baseline, they were included in that category.

3.7 STATISTICAL METHODS

3.7.1 Descriptive analysis methods for the CCMDD cohort at baseline

Data from the CCMDD, describing the cohort was merged with laboratory data for HbA1c from the NHLS. Data was analysed using Stata17. For those that had a least one HbA1c value, in the study period, median HbA1c values were compared across each descriptive variable. HbA1c values were non-normally distributed on statistical (sktest and swilk) and graphical tests, and were not able to be transformed, and are thus presented as medians with an interquartile range (IQR). Bivariable analysis between HbA1c glycaemic control category, and each variable, was performed using the Chi-square test. Data with a normal distribution are presented as means (±SD) and non-normal data are presented as medians (IQR). A confidence interval (CI) of 95% and a significance level of 0.05 was used with $p < 0.05$ considered statistically significant for all tests.

3.7.2 Descriptive and bivariable analysis methods for CCMDD-enrolled patients with a follow-up HbA1c value available

A comparison of the initial HbA1c reading, with a subsequent follow-up estimation, was made for those, for whom, at least two HbA1c readings were available within the study period. Both the first and last available reading in the study period, were described by frequency and proportion of the distribution of HbA1c values (in fulfillment of objectives one and two). Median HbA1c values were compared across each descriptive variable. HbA1c values were non-normally distributed, and were not able to be transformed. As such they are presented as medians. Bivariable analysis between HbA1c glycaemic control category, and each variable, was performed using the Chi-square test. Data with a normal distribution are presented as means

(±SD) and non-normal data are presented as medians (IQR). A 95% CI and a significance level of 0.05 was used with $p < 0.05$ considered statistically significant for all tests. Correlations and odds ratios (ORs) between sub-optimal glycaemic control at the first and last HbA1c test and intervening variables were tested, using bivariable logistic regression analysis (in fulfillment of objective three).

3.7.3 Survival analysis methods

Survival analysis was performed in fulfillment of objective four. Observations who did not have a sub-optimal HbA1c event over the study period, were right censored. The outcome of interest was years until the event of sub-optimal glycaemic control occurred. It was generated by using the date of the first failure event (i.e. suboptimal glycaemic control), for those who had a failure event in the study period, and for those right-censored, the last date of the study period was used (i.e. 30 June 2022).

Univariate analysis was performed, using Kaplan-Meier curves to analyse categorical variables, and univariate Cox proportional hazards regression was used for continuous variables (63,64). The log-rank test was used to compare survival curves across strata of categorical variables (63,64). We also calculated failure rate by period (e.g. 1st January 2018–1st January 2019) by diving the number of failures in a time period (e.g. 1st January 2018–1st January 2019), by the person-time (years) from the same time period (e.g. 1st January 2018–1st January 2019). We present the result as failure rate per 1000 person years, by multiplying the above failure rate by 1 000.

Variables were considered for use in the multivariable Cox model, if they had a p-value less than 0.25 (65). All variables, included in the final model, were considered as potential interaction terms. Interaction terms were added, one at a time, however, as no interaction terms had a significant p-value, none were included in the final model. The assumption of proportionality was tested, by using the global proportional hazards (PH) test and by including time-varying co-variates (63,64). The assumption of proportional hazards was not upheld on the global PH test. As such, an extended Cox model was built by interacting the time-varying coefficients with the natural log of time (63,64). Cox-Snell residuals were used to determine the goodness-of-fit of the models (65).

3.8 ETHICS

Ethical approval (**Appendix 3**–**Appendix 5**) was applied for and obtained through the University of the Witwatersrand's Human Research Ethics Committee (HREC; no. M220232). Data access permissions were obtained from the NDoH, CCMDD, and NHLS gatekeepers (**Appendix 6**–**Appendix 8**). Once data sets were merged and duplicate participants were identified, all identifiers were removed and stored separately to the working spreadsheet, in a password-protected file, and on a password-protected laptop.

CHAPTER 4 – EXTENDED RESULTS

4.1 INTRODUCTION

In this chapter, we present the results on the proportions of optimal glycaemic control for those who had a baseline and follow-up HbA1c test value available (objectives one and two); as well as, the results for the factors associated with sub-optimal control at patient's baseline and the last HbA1c tests in the study period (objective three). The results from the descriptive analysis of the CCMDD cohort with one HbA1c test available in the study period, as well as from the survival analysis (objective four), are found in the submissible format article in Chapter 2. Extended results from the survival analysis (objective 4), that were beyond the scope of the submissible article, are also presented in this chapter.

4.2 DESCRIPTIVE DATA FOR THE COHORT

Among the 2622 study participants with more than one repeat HbA1c test/s (**Appendix 11**), most were aged between 40–59 years (49%; 1286/2622) and were female (68%; 1772/2622). Additionally, the majority attended primary healthcare facilities (70%;1840/2622) and were prescribed monotherapy (52%; 1360/2622). The most common comorbidity was hypertension (68%; 1791/2622), with 50% of the participants (1320/2622) having a T2DM-related complication of neuropathy or nephropathy

4.3 OUTCOME DATA FOR THE COHORT

A comparison of the first HbA1c test value to the last HbA1c test value for the 2 622 case-patients with more than one test value available, showed minimal changes in glycaemic control status (**Figure 4.1**). At the first HbA1c test available, 26.5% (695/2 622) were optimally controlled, while 73.5% (1 927 /2 622) were sub-optimally controlled. At the last available HbA1c reading, 28% (744/2 622) were optimally controlled, and 72% (1 878/2 622) were sub-optimally controlled, despite their enrolment in the programme. Notably, only five LDL readings were found in the NHLS CDW for the CCMDD patient list provided. As such this aspect was dropped for further analysis in this study.

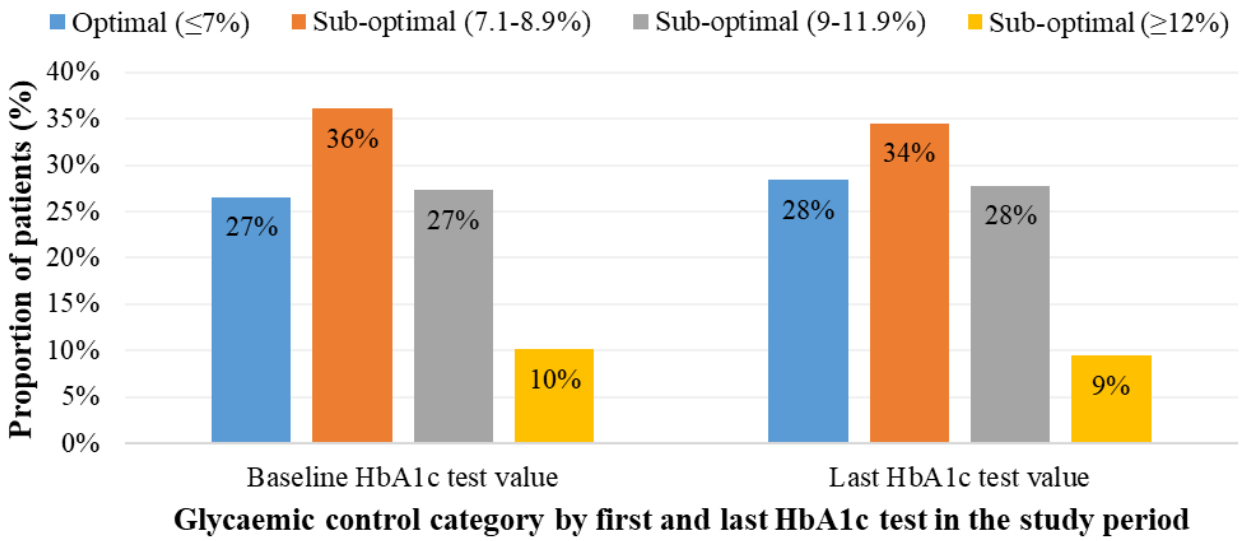

***Figure 4.1**: Distribution of HbA1c values for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa- 19th April 2018-30th Dec 2021 (N = 2622).*

Of the 695 who began optimally controlled, 35% (n = 242) changed their status to sub-optimal control over the study period. Of the 1 927 who began sub-optimally controlled, 15% (n = 288) changed their glycaemic status to optimal.

4.4 BIVARIABLE RESULTS AT FIRST AND LAST READING

Table 4.1 provides bivariable regression results, for each factor's association to sub-optimal glycaemic control, for the cohort (N = 2622) at both baseline and the last follow-up test available in the study period. Decreasing age and receiving dual versus monotherapy, were significantly positively associated with increased odds for sub-optimal glycaemic control at both baseline and last HbA1c tests in the study period. While havingT2DM-related complications (i.e. nephropathy or neuropathy) was associated with significantly decreased odds at both time points. Being female was only significantly associated with increased odds for sub-optimal control at the baseline. At the last HbA1c test, SEMDSA guideline adherence for HbA1c testing frequency, and longer CCMDD enrolment were associated with decreased odds for sub-optimal control. While attending a PHC facility versus a hospital was significantly associated to increased odds of developing sub-optimal glycaemic control.

4.4.1 Demographic Information

The odds of sub-optimal control among females was 22% (p = 0.032) and 13% (p = 0.171) higher than the odds for males, at baseline and follow-up, respectively (**Table 4.1**). Age was

significantly associated with sub-optimal glycaemic control at both baseline and follow-up. At baseline, when using those over 80 years as a reference group, those aged 39 years and under, those aged 40–59, and those aged 60–79 years had 3.8 (p = 0.000), 3.3 (p = 0.000) and 2.2 (p = 0.000) times greater odds of being sub-optimally controlled (**Table 4.1**). Similarly, at the last follow-up HbA1c test available, those aged 39 and under, between 40–59, and between 60–79 years had 2.9 (p = 0.000), 4.2 (p = 0.000) and 3.1 (p = 0.000) times greater odds of being sub-optimal controlled (**Table 4.1**). The odds of sub-optimal control increased in all age groups, from baseline to follow-up, except for those ≤39 years of age.

4.4.2 Diabetes Severity

Patients attending PHC facilities were less likely to have sub-optimal control, compared to those attending hospitals, at baseline (OR: 0.93; p = 0.423), and more likely to have sub-optimal control at the last follow-up (OR: 1.23; p = 0.029) (**Table 4.1**). Compared to patients with no reported complications, patients with nephropathy or neuropathy had lower odds of sub-optimal control, at both baseline (OR: 0.81; p = 0.017) and last follow-up (OR: 0.82; p = 0.022) (**Table 4.1**). Patients who required dual-therapy to manage their conditions, had 2.7 (p = 0.000) and 2.4 (p = 0.000) times the odds of sub-optimal glycaemic control, at baseline and follow-up, respectively, compared to those who only used one oral medication (**Table 4.1**).

4.4.3 Quality of Care

At follow-up, patients who were tested at a frequency that did not adhere to SEMDSA-recommended HbA1c testing frequency guidelines (i.e. three-monthly if sub-optimally controlled and six-monthly if optimally controlled); had 96% increased odds of having sub-optimal control, when compared to those who were tested according to SEMDSA-recommended guidelines (p = 0.000) (**Table 4.1**). At last follow-up, those who were enrolled for seven to 12 months or more than 13 months, had 10% (p = 0.459) and 17% (p = 0.046) lower odds of sub-optimal control, when compared to those enrolled for less than six months (**Table 4.1**).

4.4.4 Comorbidities

At baseline, patients with comorbidity, were less likely to have sub-optimal control, compared to those with T2DM alone. However, only multimorbidity (HIV, HPT, and T2DM) and HPT comorbidity were significantly associated with sub-optimal control (p = 0.039 & p = 0.032), with

multimorbidity patients having 31% lower odds, and those with HPT comorbidity having 25% lower odds of being sub-optimally controlled (**Table 4.1**). At follow-up, multimorbidity and HPT comorbidity were still negatively associated with sub-optimal control (OR: 0.91; p = 0.577 & OR: 0.86; p = 0.243), however having HIV with T2DM was positively associated with sub-optimal control (OR: 1.203; p = 0.401), when compared to those with T2DM alone (**Table 4.1**).

Table 4.1*: Correlates to sub-optimal glycaemic control at the first and last HbA1c follow-up test, among the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N = 2 622).*

	Baseline HbA1c test (N= 2 622)			**Last follow-up HbA1c test (N= 2 622)**		
	Bivariable Model			**Bivariable Model**		
	OR†	**95% CI‡**	**p-value**	**OR†**	**95% CI‡**	**p-value**
Sex						
Male	Ref			Ref		
Female	1.221	1.017–1.466	0.032*	1.134	0.947–1.357	0.171
Age						
≤39 years	4.785	2.497–9.171	0.000***	3.933	2.130–7.264	0.000***
40-59 years	4.278	2.630–6.959	0.000***	5.153	3.390–7.834	0.000***
60-79 years	3.173	1.952–5.159	0.000***	4.063	2.683–6.153	0.000***
≥ 80 years	Ref			Ref		
Type of facility						
PHC[a] facility	0.925	0. 764–1.120	0.423	1.226	1.021–1.472	0.029*
Hospital	Ref			Ref		
T2DM-related complication						
None	Ref			Ref		
Complications	0.808	0. 679–0.962	0.017*	0.820	0.691–0.972	0.022*
Type of therapy						
Mono-therapy	Ref			Ref		
Dual-therapy	2.744	2.281–3.302	0.000***	2.379	1.992–2.842	0.000***
Co-morbidity						
T2DM[b] alone	Ref			Ref		
T2DM and HIV[c]	0.885	0.574–1.364	0.580	1.203	0.782–1.850	0.401
T2DM and HPT[d]	0.751	0.579–0.975	0.032*	0.863	0.674 – 1.105	0.243
T2DM, HIV and HPT	0.690	0.484–0.982	0.039*	0.906	0.642–1.281	0.577
Months enrolled in CCMDD						
≤ 6 months	Ref			Ref		
7-12 months	-	-	-	0.897	0.672–1.197	0.459
≥ 13 months	-	-	-	0.828	0.688–0.997	0.046*
HbA1c testing frequency adheres to SEMDSA guideline[§]						
Yes	Ref			Ref		
No	-			1.963	1.365–2.824	0.000***

†Odds ratio, ‡Confidence interval, [a]Primary health care, [b]Type two diabetes mellitus, [c]Human Immunodeficiency Virus, [d]Hypertension; [§]SEMDSA clinical care guidelines recommend three months between HbA1c tests for those sub-optimally controlled, and six months between tests for those optimally controlled; Significance level (p-value): *p <0.05, **p <0.01, ***p <0.001.

4.5 EXTENDED RESULTS FROM THE SURVIVAL ANALYSIS

4.5.1 Survival Analysis by Year

The hazard for developing sub-optimal control was similar in 2018–2019 (failure rate: 152.02 per 1000 person-years, 95% CI= 115.22–200.58) and 2020–2021 (failure rate: 156.82 per 1000 person-years, 95% CI= 125.96–195.24) time periods and, was somewhat higher in the 2021–2022 (failure rate: 162.96 per 1000 person-years, 95% CI= 124.81–212.78) time period. Comparatively, the 2019–2020 time period (failure rate: 112.67 per 1000 person-years, 95% CI= 85.40 – 148.66) had a lower failure rate (**Table 4.2** and **Figure 4.2**). Notably, the 2017–2018 (failure rate: 51.79, 95% CI= 25.90 – 103.56) and 2021–2022 time periods only consisted of two and six months, respectively. The median time between tests in the level 4-5 lockdown periods (i.e. 27th March 2020–1 June 2020) was 11.8 (6.4–14.9) months versus 12.1(8.9–20.1) months in 0-3 level lockdown periods. Similarly, the median HbA1c test value in the level 4-5 lockdown period was 6.4% (95% CI= 6–7.3) versus 6.7% (95% CI= 6.2–7.3) in levels 0-3 periods.

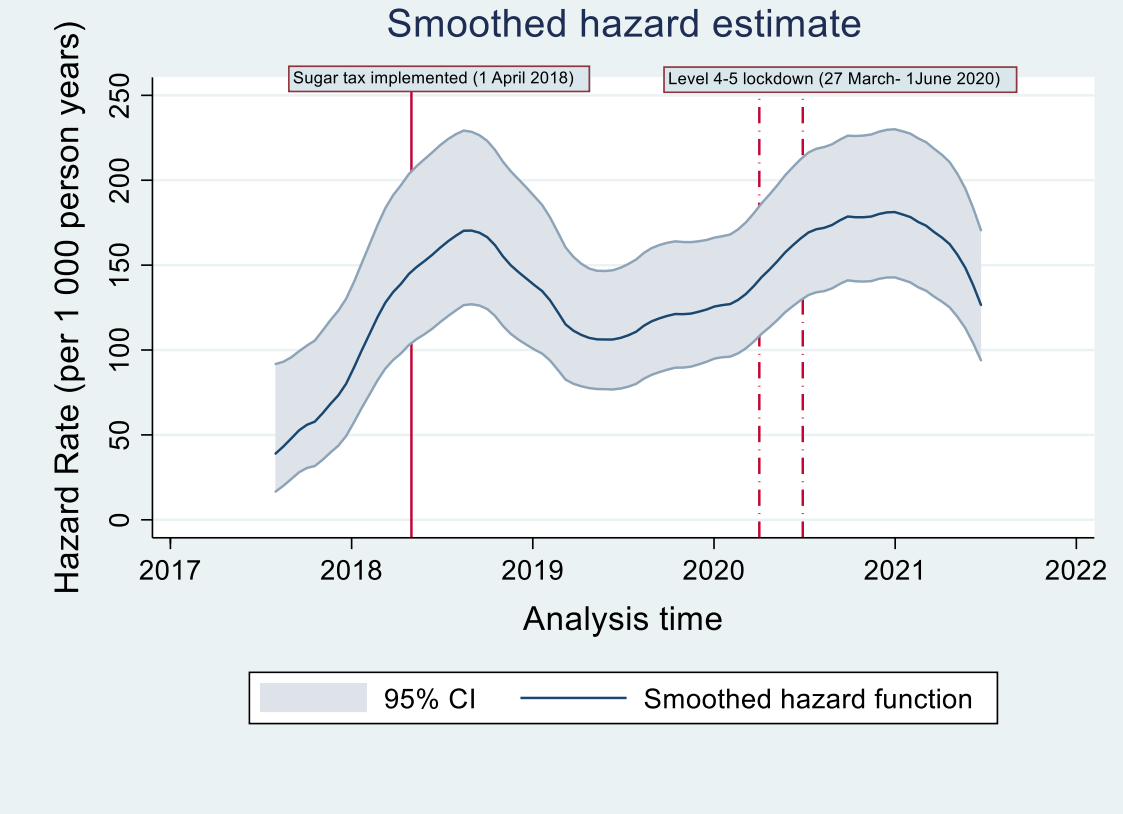

Figure 4.2*: Smoothed hazard (sub-optimal glycaemic control) rate estimates for the Central Chronic Medicines Dispensing and Distribution programme cohort, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (NHLS window:18th October 2017–30th June 2022) (N = 242); CI, Confidence interval*

CHAPTER 5 – CONCLUSION

5.1 INTRODUCTION

In this chapter we will discuss the results from our study's descriptive analysis and survival analyses. In this study, we firstly aimed to determine whether adult T2DM CCMDD-enrolled patients, collecting chronic medication from community PuPs, were optimally controlled for their T2DM at enrolment into the CCMDD programme and at last HbA1c reading. Our results are presented and are placed in context using existing literature.

Secondly, we aimed to determine which factors were associated with sub-optimal control and time to sub-optimal control, between 2018 and June 2021, in the eThekwini district, KwaZulu-Natal. Our results are presented and are compared and contrasted to other relevant studies.

We then reflected on our studies' limitations and strengths. Finally, we made recommendations for the CCMDD, the NDoH and for future studies, based on our findings.

5.2 DISCUSSION

5.2.1 Descriptive analysis of HbA1c and LDL testing

We found that of the cohort enrolled in the eThekwini CCMDD who received oral hypoglycaemic medications (41 145), between 2018–2021, the majority, 81% (33 185), had no HbA1c test available in the three-year study period. Similar results were found in an audit study conducted at a diabetes clinic in a KZN regional hospital (2011) and at PHC facilities in the Western Cape (2015–2020), where 76% and 70% of T2DM patients, respectively, had no HbA1c test in the preceding 12 months (66,67). This seems to indicate that HbA1c testing remains an issue, despite the existence of the SEMDSA guidelines for quality of care.

We also found, that of those with an initial result available, only 33% (2 622/7 960) had a follow-up HbA1c test available in the NHLS, between the 18th October 2017–30th June 2022. Similarly, a study conducted in GP, between January 2015 to December 2018, found that 26% of patients with a first-ever HbA1c test in the NHLS, had follow-up results over their four-year study period (68). Only 24% of T2DM patients had a repeat HbA1c test available, in a 12 month review period, in a 2011 audit study in a KZN regional hospital (66).

Additionally, in our study, only 1.7% (695/41 145) of the CCMDD cohort receiving an oral hypoglycaemic agent, had an initial optimal glycaemic reading (at their reading closest to enrolment into the programme) and at least one follow-up test, to be included in the survival analysis.

Furthermore, we found that the median time between HbA1c tests, for those who had at least one follow-up HbA1c reading, was 13 months (range: 10–19) for those optimally controlled and 12 months (range: 8–19) for those sub-optimally controlled. We expected to find more frequent testing being performed, in line with the three-monthly or six-monthly testing as set out in the SEMDSA and STG guidelines, respectively (4,16). A similar finding was described by Kone et. al. for HbA1c testing in GP, where the median testing interval was reported as 11 months (95% CI: 5–16), whether the control status was optimal or sub-optimal (68).

We had sought to assess LDL measures for this cohort, as LDL measures can be used as an intermediate target for cardiac health, as it is an additional risk factor for developing macrovascular complications causing coronary artery disease (CAD) in those with T2DM (4). However, despite the SEMDSA, recommending annual testing of LDL for PLWT2DM, there were only five measures in total extracted from the NHLS. As such, we had to drop this component from the analyses. While seemingly inexplicable, similar findings are not unheard of. A 2011 KZN regional hospital audit, of people attending a diabetes clinic, found that while 74% of T2DM patients had a total cholesterol test performed, no patients had LDL tests performed in the 12 months preceding the audit date (66).

5.2.2 Proportions achieving optimal control at enrolment and at last recorded HbA1c test

We estimated that of those receiving medication through the eThekwini CCMDD programme, with at least one HbA1c available, only 27% (2 147/ 7 960) had optimal glycaemic control at the HbA1c reading closest to CCMDD enrolment. Of those that had at least one follow-up HbA1c reading available, 27% (695/ 2 622) had optimal glycaemic control at their first available HbA1c test, with 28% (744/ 2 622) optimally controlled at their last available HbA1c test in the study period. This finding is of deep concern and pinpoints an unmet need at this level of the cascade of care. It will need to be addressed if the NDoH aims to meet the SA National strategic plan's target of 50% of those receiving treatment to achieve glycaemic control by 2030 (39).

These results concur with a PHC facilities file audit, conducted in Tshwane in 2019, by Ngassa Piotie et al., which revealed that only 29% of patients enrolled in CCMDD had optimal glycaemic control (57). There has been one population-based study in South Africa, by Stokes et al. in 2017, using data extracted from the SANHANES (2011–2012), that estimated that of those treated, 51% had achieved optimal glycaemic control (48). This differs considerably from the findings in our study. Potentially, levels of sub-optimal control, among those receiving medication, have increased considerably over time, or the population of eThekwini may not be representative of South Africa as a whole. Also, the SANHANES survey included insulin-users and did not differentiate between type 1 and type 2 diabetes, as well as, including those aged over 15 years of age (69).

However, our finding, of the proportion optimally controlled, fell within the range found in previous clinical audit studies (15.3%–30.7%) across South African provinces (52–56,58). They consistently report small proportions of T2DM patients reaching glycaemic targets, across primary (i.e. 19.3% at Hillbrow Clinic in 2017 and 27% across Tshwane PHCs in 2015) and tertiary levels of care (i.e. 20.1% at Umtata General Hospital in 1999, 30.7% at GP academic hospitals in 2009, 15.4% in Port Shepstone Hospital in 2017, and 15.3% at Helen Joseph Hospital in 2020) (52–56,58).

While our findings are congruent with these past studies, we expected levels of optimal control to be significantly higher in this cohort, as they had to have achieved a stable condition to be enrolled into the CCMDD programme. This discrepancy may be partially explained by this study defining optimal glycaemic control status using an HbA1c value of ≤7%, while the CCMDD defines a stable condition using a FPG value of < 7mmol/L (43). We chose to use HbA1c in this study as it is recommended as the gold standard for the monitoring of glycaemic control by the IDF (1), as it indicates glycaemic control over a few months (2,6). Whereas, FPG is a spot measure and is easily influenced by glucose intake before the reading. Studies have found that FPG and HbA1c measures may not be congruent (1,2).

Additionally, while the median time between enrolment into the CCMDD, and the first available HbA1c test, was three months preceding enrolment; there was a wide 95% CI of 13 months before to 10 months after the CCMDD enrolment date. As such, there may have been a change of state between enrolment and the first laboratory test available for HbA1c in this study.

Nevertheless, our study estimates that 72−73% of patients enrolled in the eThekwini CCMDD programme are sub-optimally controlled. This is problematic as the CCMDD's mandate, is to provide easier access to medication for stable patients, who inherently require fewer encounters with healthcare providers (43–45). However, it appears as if the programme is not consistently, correctly targeting stable T2DM patients. As a result, these sub-optimally controlled patients are continuing to collecting their medications at community-based PuPs, and are only attending their clinics bi-annually. Thus, negating the SEMDSA's recommended three-monthly clinical check-ups, for sub-optimally controlled patients (4). This represents many missed opportunities to intervene, educate and improve glycaemic control and T2DM-related health outcomes for PLWT2DM in eThekwini. Sub-optimal control may be contributing an increased risk for T2DM-related complications and to premature deaths. Our study suggests that the definition for enrolment into the CCMDD may need to be reviewed. More pertinently, however, definitions and protocols need to be developed for patients to exit the programme when they become sub-optimally controlled, for the CCMDD to achieve maximum benefit for their patients.

5.2.3 Factors associated with sub-optimal control and time to sub-optimal control

Sub-optimal control is associated with non-compliance with HbA1c testing interval guidelines

Non-adherence with SEMDSA's monitoring guidelines (i.e. testing within three months for those sub-optimally controlled and within six months for those optimally controlled) was significantly associated with being sub-optimally controlled in the bivariable analysis (OR: 1.96, 95% CI: 1.365- 2.824, p-value: 0.000) and adherence with SEMDSA's guidelines was significantly protective for the development of sub-optimal glycaemic control in the survival analysis (aHR: 0.463, 95% CI: 0.237−0.905, p-value = 0.024).

Our findings are in agreement with international studies that have shown that more frequent testing was associated with reduced HbA1c readings, improved glycaemic control, and reduced T2DM-related complications (70–73). An Australian study, monitoring longitudinal HbA1c values in T2DM patients attending GP practices between 2013 to 2018, found that high adherence to the Australian guidelines for HbA1c testing intervals, at three-monthly for those sub-optimally controlled and six-monthly for those optimally controlled, resulted in patients remaining controlled over time. While low adherence to guidelines resulted in increased HbA1c readings, sub-optimal glycaemic control and higher risk for chronic kidney disease (70).

A study from the United Kingdom (UK), compared glycaemic control in patients receiving three-monthly testing to those receiving annual testing, using data from clinical laboratories, and determined that three-monthly testing was associated with a reduction in HbA1c (by 3.8%) versus annual testing that increased HbA1c (by 1.5%) (73). A study in India spanning the years 2003 to 2012, compared six-monthly testing to annual testing, and found that those with irregular follow-up patterns had twice the glycaemic burden, as well as twice the risk for developing retinopathy and nephropathy (71). A further study in the USA determined that testing at an interval of two to three months was optimal to achieve a maximal downward change in HbA1c; whereas, testing at any time over six months, resulted in upward changes in HbA1c (72).

Our study suggests, that despite the policies being in place for care standards at Primary and hospital levels of health care, the recommended policy is not being implemented. This may be partially explained by the time period of this study, during a time when CMMD changed their activities due to COVID-19. However, the similar results found in Tshwane pre-COVID (2019) suggest other factors may be at play. Clinical inertia has been suggested as a factor in the poor management and outcomes of T2DM patients (54). Additionally, a lack of clinician awareness of the guidelines may be a factor. A previous audit at Tshwane PHCs, by Webb et. al. in 2019, found that the SEMDSA guidelines were not known to any of the clinics audited (74). And the NDoH guidelines on diabetes care were not available in two-thirds of the clinics (74). Resource allocation for diabetes care, in South Africa, has been somewhat neglected, in light of the communicable disease burden (54,74), thus resulting in a healthcare system, that is ill-equipped for chronic disease management.

Dual-therapy is associated with increased risk for sub-optimal control

Additionally, we found that patients receiving dual-therapy were at increased risk for developing sub-optimal control. Our bivariable analysis revealed that patients who required dual-therapy to manage their conditions, had 2.7 ($p = 0.000$) and 2.4 ($p = 0.000$) times the odds of sub-optimal glycaemic control, at baseline and follow-up respectively, compared to those who only used one oral medication. These findings concur with results obtained in a study on the determinants of glycaemic control for PLWT2DM in Lebanon where those using dual-therapy compared to monotherapy had twice the odds of being uncontrolled (OR: 2.35, 95% CI: 1.58–3.50) (75). Similarly, our survival analysis estimated an adjusted hazard for those using dual-therapy as 50 times higher than the hazard among those using monotherapy ($p = 0.002$). This result could be

attributed to dual-therapy being used only for patients who failed to attain optimal glycaemic control with metformin alone. As such, this group may reflect individuals with higher rates of past failures or vulnerabilities to achieving glycaemic control, before they obtained a stable status for CCMDD enrolment. While associations between sub-optimal control and insulin use, when compared to oral hypoglycaemic medication use, are well documented (75–77), we could not address this in our analyses, as the CCMDD does not dispense insulin.

Attending PHC facilities is associated with increased risk for sub-optimal control

Moreover, we found that while the type of facility the patient attended, was not significantly associated to developing sub-optimal control at baseline, the combined effect over time was that of a decreasing hazard, for those attending hospitals. The GP-based HbA1c laboratory data study, had a similar finding. They found that those attending hospitals had a higher likelihood of achieving good control compared to those attending PHC facilities (68).

This observed effect could be linked to overburdened workloads and under-resourcing at PHC facilities. Currently, HIV and TB cases are mostly managed at PHC level, placing a large burden on these facilities (78,79). Further stress has been placed on the health system, by the rising NCD disease burden. Integrated Chronic Disease Management was initiated by the NDoH, to create a single, integrated, person-centered approach to health care management at PHC level (78,79). Thus avoiding managing patients in disjointed vertical silos for a single disease at a time; but rather allowing for integrated diagonal management for multimorbidity (78,79). However, studies suggest that there are a lack of resources (medication, blood tests, NCD-trained health practitioners, and central electronic health records), infrastructure (clinics have outgrown their intended case-loads), and a willingness for healthcare providers to adapt, presently, to support integrated NCD management at PHC level (42,78,80). Thus resulting in under-treatment and poor outcomes for those with NCDs, such as diabetes, at PHC level (78).

Other factors associated with sub-optimal control

In our bivariable analysis increasing age and having hypertension comorbidity or multimorbidity (HIV and HPT) was protectively associated with sub-optimal glycaemic control. This may be due to those with other health conditions, or with ailing health associated with aging (i.e. falls, dementia, depression, urinary tract infections or incontinence), having more opportunistic clinical encounters, where they may receive advice on managing their T2DM (81). Other study's

looking at factors associated to glycaemic control, have found increasing age to be a protective factor for sub-optimal control (76,77). Survival bias may play a role, in that those who have survived to the age of 80 years, with a diagnosis of T2DM, may be more proficient at self-care and self-management. However, neither factor was significantly associated with developing sub-optimal control in our survival sub-analysis.

We found no significant association between T2DM-related complications (i.e. neuropathy or nephropathy), and sub-optimal glycaemic control. Which is in contrast to findings from a study conducted in Lebanon, where neuropathy was highly associated with sub-optimal glycaemic control (OR: 2.08, 95% CI 1.11 – 3.90) (75). In our bivariable analysis, we found that being female increased the odds of having sub-optimal control at baseline (OR: 1.22; 95% CI: 1.017 – 1.466; p = 0.032). This finding agrees with a GP-based HbA1c laboratory data study, that found males to have a higher likelihood of achieving good control (aHR: 1.16; 95% CI: 1.12 – 1.20; p < 0.001) (68). However, there was no longer a significant association at the last HbA1c test in the study period. Similarly, in our survival analysis, we found no significant association between sex and sub-optimal control.

An unintended finding was that of decreased hazards for developing sub-optimal control in the 2018 – 2019 time period. The decrease may be related to the introduction of a sugar-tax on beverages in South Africa, on the 1st of April 2018 (35,36). A study on daily grams of sugar consumed, calories consumed, and volume of sugar-sweetened beverages consumed found a reduction across all fields in the post-implementation period (April 2018 to March 2019), which correlates to the trend of decreased hazard for sub-optimal control observed in this study (36).

An increased hazard in 2020 – 2021 and 2021 – 2022, compared to 2019 – 2020, correlates to periods of hard lockdown measures due to COVID-19 in South Africa. During level four and five lockdowns, peoples' movements were severely restricted and scheduled chronic care visits were de-escalated, to allow for the re-allocation of services to those requiring acute COVID-19 related care (82,83). Implementation of CCMDD's activities also changed during the pandemic, to reduce risk of COVID-19 exposure in this higher risk group and to minimize close contact between patients (84). Prescriptions were extended from two to three months for collection, and clinic visits were extended from six-monthly to annually (84). A systematic review conducted in 2022, which included 11 studies totaling 16 895 participants, which found that HbA1c levels significantly increased by 0.34% (95% CI: 0.30% – 0.38%) when comparing values for those in

COVID-19 lockdown to a the same groups' values pre-COVID (85). However, in this study, those tested during the COVID-19 level 4-5 lockdown periods had similar HbA1c testing intervals and similar test result values, as those tested in level 0-3 lockdown periods.

5.2.4 Using existing data to establish T2DM-realted baselines and data registries

Finally, in a broader sense, this study shows that we can use available secondary retrospective data within the CDW, to assess the current deficit in the cascade of care, and establish baselines for the NDoH and Provinces to assess their path towards the 2030 NSP targets. As there is no reliable, central data repository for T2DM in South Africa, linking CCMDD data to laboratory test data, to allow for monitoring and evaluation, of enrolled patients glycaemic status.

Based on our study, the CCMDD can be encouraged to adopt an approach in line with the Western Cape's medication dispensing programme. It grew to include data sources from tertiary and primary level facilities for clinical data, pharmacological data, laboratory diagnostic data, and mobile health data, to establish the Western Cape Provincial Health Data Centre (WCPHDC) in 2015 (86). They developed a unique identifier to link individual-level patient data from the various data sources using probabilistic scoring based on identification documents or hospital file numbers, and is supplemented by fuzzier comparators (86). This consolidated, patient-level data has allowed for improved patient care in terms of tracking patient encounters through the health system, understanding comorbidities, retention in care, control status, and patient outcomes as well as providing an opportunity for follow-up and action through alerts (86). The WCPHDC has previously suggested that, pending national unique identifiers for linkage, this model could be generalized nationally, as data sources or comparable alternatives are available (86).

5.2.5 Limitations

The initial study period, from the CCMDD's establishment (2014) to 2021, was not possible. This was due to data inaccessibility prior to 2018, when CCMDD changed service-providers.

Furthermore, there is a paucity of estimates for the proportion of PLWT2DM, receiving treatment, in eThekwini. Based on SANHANES-1 (2011–2012) data, it was estimated that 94% of South Africans who received a T2DM diagnosis, were being treated with either oral hypoglycemic medication or with insulin (48). However, the CCMDD does not enroll PLWT2DM who use insulin, and as such, this portion of the population, who likely have more

progressive disease, are not represented in this study. Without available estimates for eThekwini, we are not aware, of what proportion of PLWT2DM, the CCMDD-enrolled patients represent. Additionally, there were limited HbA1c test results available, thus hampering generalizability to the entire CCMDD population in eThekwini. As such, these results must be interpreted with caution.

Factors known to be associated with sub-optimal glycaemic control were not available in either data set. As such, factors such as, race, other co-morbid conditions (such as TB), obesity measures (i.e. weight, height, BMI), lifestyle factors (i.e. smoking, alcohol use, diet, physical activity indices), clinical measures (i.e. BP, cardiac or kidney function markers), genetic factors, socio-economic factors (i.e. income level, education level and health literacy level), self-efficacy, medication compliance, and duration of diabetes were not able to be included.

Despite these limitations, our study's strengths were using data from 13 hospitals and 107 PHC facilities in eThekwini, thus suggesting a good representation of the general CCMDD-enrolled population in eThekwini. Furthermore, this was also the first study of CCMDD-enrolled patients in eThekwini. Lastly, despite the CCMDD being a large public health programme, this was the first time CCMDD-enrolled patients were linked to their clinical HbA1c results, to monitor and evaluate glycaemic control over time.

5.3 RECOMMENDATIONS

5.3.1 Recommendations for the low number of HbA1c and LDL tests available

The low number of HbA1c and LDL test available for this cohort, as well as the long periods between HbA1c tests, sparks further questions. We suggest patient file audits for a sample of patients from this cohort, to confirm that the HbA1c and LDL tests matched from the NHLS were accurate, and to uncover any underlying issues with data quality or data linkage. Qualitative interviews with DoH stakeholders at eThekwini district or KZN Provincial level, may provide further understanding of any budgetary constraints or other barriers that may have limited more frequent HbA1c and LDL testing. Interviews at facility-level are recommended to discover if a mismatch in facility HbA1c and LDL testing protocols, compared to NDoH and SEMDSA recommendations exists, or if point-of-care devices or other glycaemic control tests, such as FPG are being favored over HbA1c laboratory testing. Furthermore, for future studies, we recommend

more advanced probabilistic matching for NHLS data, to ensure no cases are being missed at that level. We also recommend requesting total cholesterol values for future studies, to understand the low number of LDL-cholesterol tests. However, SEMDSA care guidelines recommend a fasting lipogram, which includes a LDL-cholesterol test, annually for PLWDM (3-monthly if in T2DM cases of lipid abnormality) as it important for assessing risk for CVD (4). The cost of a direct LDL-cholesterol test is 25% of a full lipogram test (87).

5.3.2 Recommendations for the below-target proportions achieving optimal control

As 73% of CCMDD-enrolled patients are sub-optimally controlled at the HbA1c reading closest to their enrolment, we recommend that the CCMDD review their enrolment criteria. We recommend using two consecutive HbA1c test values (<7%) to assess CCMDD enrolment eligibility, rather than the two consecutive FPG test values currently being used. This is in agreement with previous recommendations from Ngassa Piotie et. al. (1).

Additionally, as 72% of CCMDD-enrolled patients were sub-optimally controlled at their last recorded HbA1c test in the study period, we recommend that the CCMDD develop an exit protocol, for those that become sub-optimally controlled. Thus, a source of regular feedback on HbA1c glycaemic control status, should be incorporated into the CCMDD programme. This is critical in the context of diabetes, which is a progressive disease by nature. As the disease progresses, medication management (i.e. adding insulin to the regime) and the prevention/management of T2DM-related comorbidities must be escalated accordingly. If there is no feedback of glycaemic control status to the programme, clinical and patient inertia may well be compounded. We recommend individual-level data linkage, to NHLS test results, in line with the WCPHDC (86). Alerts from laboratory sources, when patients change status from optimal to sub-optimal, is an essential feedback mechanism that needs to be put in place within the CCMDD programme, to ensure the correct enrolment definition of stable patients is adhered to at enrolment, but also, critically, that the patient is eligible to continue being enrolled.

Alternatively, the use of point of care HbA1c devices and mHealth applications by CHWs in home, PuP, or counseling group environments, to screen these patients, at community-level, according to the SEMDSA testing interval guidelines is recommended. These results would then enable the CCMDD to monitor glycaemic control for those enrolled. Technological innovations

and mHealth (mobile phone health) have been promoted by WHO (88) and have assisted community health workers (CHWs) to help people manage their NCDs at monthly home visits.

An example of this comes from rural Guatemala, where the use of a smart phone application, was used as a tool to provide algorithmic decision support for clinical decision-making, to assist CHWs in the monthly management of their patients' diabetes, thus alleviating the burden of clinic-based healthcare workers through task sharing (89). In South Africa, CHWs have been used over the past several years, in maternal and child health; as well as, in communicable diseases e.g., HIV, tuberculosis, and in malaria; to provide an extension of care at community-level, in response to the human resource crisis (41). As such, we are ideally placed to extend their training, skill sets, and scope of practice to encompass diabetes and other NCD monitoring and management (41). This would involve updating the CHW curriculum to include HbA1c point of care testing (90). This approach would align well to the NDoH's Integrated Chronic Disease Management model (79). The South African demonstration site for the HealthRise project, (2017 –2018) in seven PHCs from the KZN sub-districts of Msunduzi, uMshwathi, and Mkhambathini, demonstrated the role CHWs play in bridging considerable gaps in screening, linking patients to care and in educating patients on self-management (91).

Otherwise, self-management in this cohort must be emphasized, if glycaemic control is only being monitored annually, at clinic-level. Health literacy, socioeconomic status (70), and self-efficacy (57) have been previously described in the literature as factors affecting adherence to diabetes care guidelines and self-care. In South African, glucose test strips, required to self-monitor random glucose levels for home-based self-care, are not included in the EML and thus are not available for free through public health care facilities (16,54,74). Thus, to improve self-care for PLWT2DM, in the South African context of socioeconomic inequalities and socioeconomic challenges, the EML would need to be amended, to include the provision of state-funded glucose test strips and units. Data from large-scale studies such as the GUIDANCE study in Europe, revealed that participants who were accurately aware of their glycaemic status, have significantly lower HbA1c readings (92). As such, if the EML was extended to include glucose monitoring strips for PLWT2DM, we may also observe greater proportions of sustained optimal control, among those receiving oral hypoglycaemic medication through the CCMDD.

In addition to self-monitoring, continuous patient education and support, potentially through mobile applications, can assist in empowering PLWT2DM to self-manage and control their

conditions. A study in the WC, by Mash et. al. between 2019 and 2022, found that implementing the GREAT4Diabetes WhatsApp Chatbot during COVID-19, when in-clinic education and counseling for T2DM ceased, resulted in good uptake (51% listening to all messaging), and self-reported improvements in self-management (71%), diet (76%), physical activity (54%) and in their confidence-levels about their diabetes self-care (88%) (93). It may be worth investigating if developing such an application, within the CCMDD, may assist in improved proportions maintaining a stable T2DM condition, to offset less frequent encounters at clinics, by virtue of being enrolled in such a programme. Thus, maximizing medication accessibility as well as improving clinical outcomes and self-care. It has also been suggested, previously, that screening for self-efficacy, as an additional CCMDD enrolment criteria, may improve proportions that remain optimally controlled over time, by ensuring that those enrolled can self-manage their conditions (57).

A detailed cost-benefit analysis, for each approach (i.e. person-level data linkage, using mHealth and CHW, or promoting self-care), against the potential cost of managing T2DM-related complications, associated with 74% of this cohort being sub-optimally controlled, is advisable. While training and development of mHealth applications will require a set-up and maintenance fee, ultimately, the cost of treating T2DM-related complications due to sub-optimal control, may be far costlier. In India, a basic cost assessment was performed and estimated that the cost of increasing encounter frequency, would be offset by the saving as a result of reduced T2DM-related complication management (71). Basu et al (2021) created a microsimulation, where LMIC achieved targets of 80-80-80 for diabetes; meaning 80% of patients with diabetes diagnosed, 80% of those diagnosed on treatment, and 80% of those on treatment achieving recommended glycaemic targets; and deduced that the resulting reduction in cardiovascular events, would offset the increased cost of treatment, resulting in $1 362 cost-per-disability-adjusted life year (DALY) averted (49). A study from cascades of care from Poltava in Ukraine in 2020 also estimated that if 1% more patients achieved sustained optimal glycaemic control, there would be a reduction in patient monitoring costs of $10 373, annually (94). This amount would cover the cost of adherence counseling for half of their patient load (94).

As this is the second study, within different sub-districts (57), indicating high proportions of sub-optimal control among CCMDD-enrolled patients, we recommend further studies in other

districts, and at provincial and nationals level to confirm these findings, and to allow for a larger sample sizes.

5.3.3 Recommendations for sub-groups at increased risk for developing sub-optimal control

We recommend facility-based audits and further qualitative studies to establish if facility-specific barriers to care exist, for HbA1c testing, in eThekwini. Resource allocation for further training for clinicians on the SEMDSA and NDoH guidelines for care for PLWT2DM with emphasis on the critical nature of achieving a stable, optimal glycaemic condition for this population, is essential, to improve compliance to the HbA1c and LDL testing frequency guidelines.

Additionally, as resources for T2DM are constrained, we recommend more feasible solutions to increase the frequency of clinical encounters and HbA1c testing. These include pivoting the role of existing CHW, using mHealth technologies, as elaborated in 5.3.2 above. Group education and counseling is another solution. Allerton and Mash, found a 1.1% decrease in mean HbA1c among sub-optimally controlled PLWT2DM attending Khayelitsha Community Health Centre, concluding that the main mechanism leading to the decrease lay within the introduction of group diabetes education (however they also received monthly encounters with doctors and increased HbA1c testing frequency) (95).

Furthermore, our results suggest that those prescribed dual-therapy may require closer monitoring within the programme, or may benefit from more frequent clinical encounters. CCMDD protocols could be reviewed for this patient sub-group. Self-efficacy questionnaires as an additional CCMDD enrolment criterion is recommended.

5.3.4 Additional recommendations

For future studies, additional monitoring tests could be requested from the NHLS CDW, to assess T2DM-related complications such as kidney-disease markers or markers for cardiac disease. We also suggest that the National Cancer Registry (NCR)’s method of hot-deck imputation, be used in future studies, to assist in determining the impact of race on sub-optimal control (68). This method correlates individuals with unknown race to a reference database of surnames, for which race is known, providing reasonable accuracy for those with missing race data (96).

5.4 CONCLUSION

In conclusion, of the adult T2DM CCMDD-enrolled patients, in eThekwini, between 2018 and June 2021, who were collecting chronic medication from community PuPs, 27% and 28%, were optimally controlled for their T2DM at enrolment and at the last HbA1c reading, respectively. We demonstrated that existing secondary data, housed in the NHLS CDW can provide baseline data, to assess gaps in the diabetes care cascade at district-level; and could be replicated in other districts, or at provincial, or nationally levels. Our findings, and future findings, can assist the NDoH to monitor their progress towards the NSP target, of 50% on treatment achieving glycaemic control, by 2030. Additionally, our study provides good supporting evidence for increased HbA1c testing frequency in this cohort, and the need for feedback of these values to the CCMDD. It also provides evidence, for additional care to be taken when enrolling patients on dual-therapy, who may be more vulnerable to developing sub-optimal control, such as perhaps, incorporating a self-efficacy score as an additional criterion for enrolment. This knowledge can assist in the successful implementation and further development of the CCMDD.

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APPENDICES

APPENDIX 1: PLAGIARISM DECLARATION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

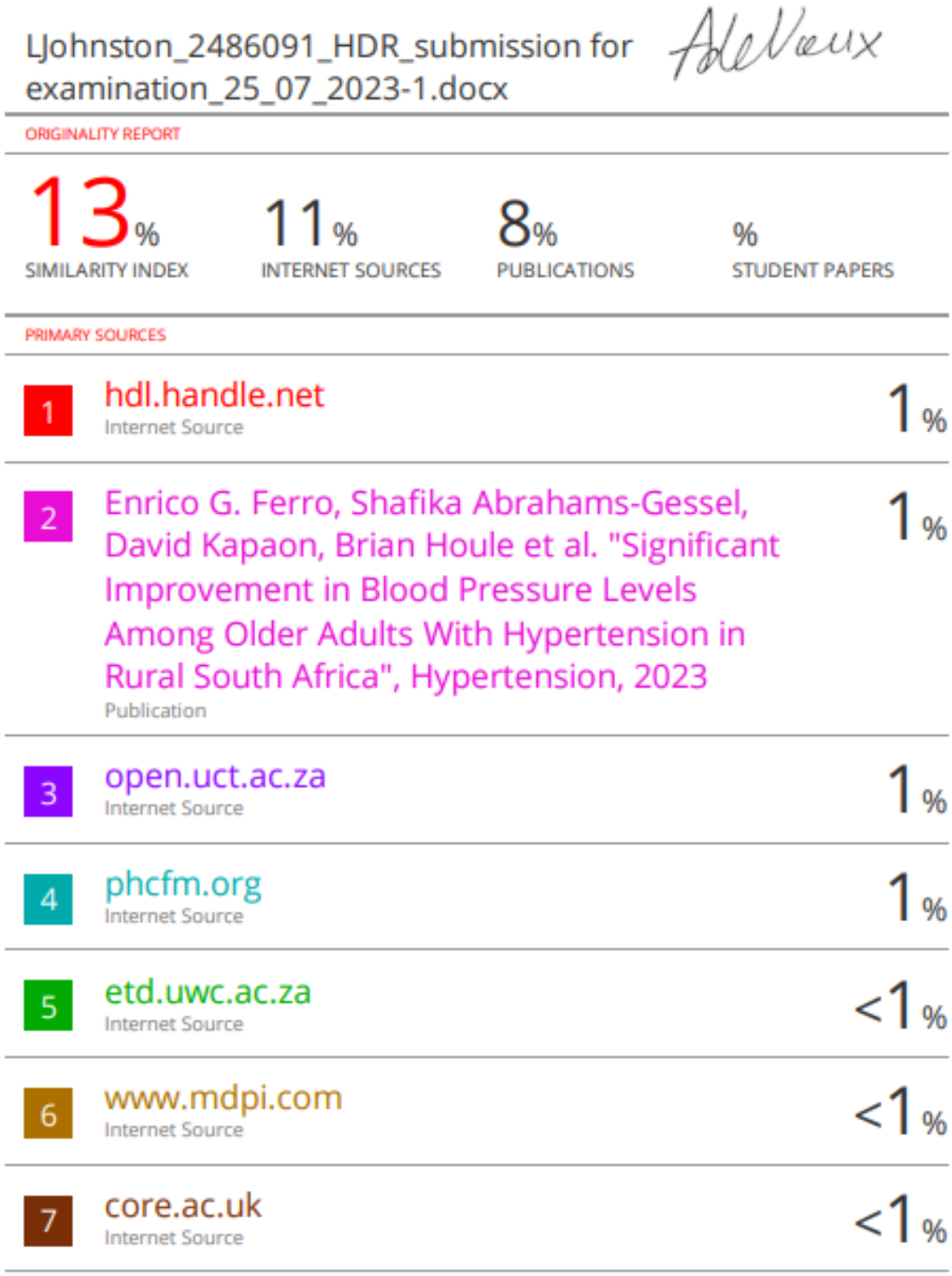
I Leigh Johnston (Student number: 2436091) am a student registered for the degree of MSc Field Epidemiology in the academic year 2023.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 16/06/2023

APPENDIX 2: TURNITIN COVER PAGE



LJohnston_2486091_HDR_submission for examination_25_07_2023-1.docx

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APPENDIX 3: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms LC Johnston

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220232

NAME: (Principal Investigator)	Ms LC Johnston
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Determinants of sub-optimal glycaemic control amongst patients enrolled in a medicine dispensing programme in KwaZulu Natal: a longitudinal study, 2014-2021*
DATE CONSIDERED:	2022/02/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs A de Voux, L Kuonza and S Singh
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/04/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

APPENDIX 4: WITS APPROVAL LETTER FOR CHANGE OF RESEARCH TITLE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

08 February 2023
Person No: 2486091
TAA

Miss LC Johnston
PO Box 506
Gallo Manor
2052
South Africa

Dear Miss Leigh Johnston

Master of Science in Epidemiology: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Science in Epidemiology** has been approved:

From:	**Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2014-2021**
To:	**Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2018-2021**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 5: WITS HREC APPROVAL OF CHANGE OF RESEARCH TITLE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms LC Johnston

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220232

NAME: (Principal Investigator)	Ms LC Johnston
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Determinants of sub-optimal glycaemic control amongst patients enrolled in a medicine dispensing programme in KwaZulu Natal: a longitudinal study, 2018-2021* Amended project title noted on 2023/02/20
DATE CONSIDERED:	2022/02/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs A de Voux, L Kuonza and S Singh
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/04/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX 6: CCMDD DATA PERMISSION

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Private Bag X828, PRETORIA, 0001 Dr AB Xuma Building1112 Voortrekker Road, Pretoria Townlands 351-JR, PRETORIA, 0187 Tel (012) 395 8000, Fax (012) 395 8918

24 March 2022

Members of the Wits HREC

RE: Permission to utilise CCMDD data for a study as defined by the Data Users Agreement: National Department of Health - "Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2014-2021" conducted by Leigh Johnston.

This letter concerns the research study of Leigh Johnston, affiliated with the University of Witwatersrand and the National Department of Health (NDoH) Non-communicable disease (NCD) directorate as a resident in the South African Field Epidemiology Programme (SAFETP). I am formally writing, as the head of the Central Chronic Medicine Dispensing and Distribution (CCMDD) Programme to indicate our awareness of the MSc research project proposed by Ms. Johnston, titled:

"Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2014-2021".

I am aware that Ms. Johnston has obtained provisional ethical approval from the Wits Human Research Ethics Committee (Medical) for the above-mentioned study and as such, as the head of the CCMDD programme and data gatekeeper, I give Leigh Johnston permission to access data from the CCMDD to conduct her research from April 2022 to December 2023, pending full ethical approval. She will be accessing secondary data from the CCMDD programme and merging it with clinical data for glycaemic control from the National Health Laboratory Service (NHLS). We have fully reviewed her protocol and she has our permission to access the CCMDD data to answer her research questions pertaining to determining those optimally controlled for their diabetes within the CCMDD programme as well as determining factors associated with and time to sub-optimal glycaemic control.

The results from this study will be shared with the CCMDD,NDOH to further strengthen and develop the programme as well as supporting the need for a central data repository for diabetes data to strengthen monitoring and evaluation efforts.

You are welcome to contact me at Maggie.Munsamy@health.gov.za or telephonically at 0825509166

Ms M Munsamy

CPSI INNOVATOR OF THE YEAR

NHI Technical Specialist: Contracting
Head: CCMDD

APPENDIX 7: NHLS DATA PERMISSION

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6155
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

12 April 2022

Applicant: Leigh Johnston
Institution: NHLS / NICD
E-mail Address: leighj@nicd.ac.za
Cell: 082 379 2428

CC: Lazarus Kuonza, Alex de Voux

Project Title: Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2014-2021
Reference Number: PR2223694

Research Application Type(s):
1. Request for Data

RE: APPROVAL LETTER: REQUEST TO ACCESS NHLS RESOURCES FOR RESEARCH PURPOSES

This letter serves to advise that the application requesting permission to conduct the above-mentioned research using the listed NHLS resources has been reviewed and **"Approved"**. Please note that the approval is granted on the condition that you comply with the NHLS Research Material and Data Access Policy and requirements stated below.

1. All material and data requested shall be used as per the research protocol submitted to the NHLS and as approved by the relevant Health Research Ethics Committee (HREC) in South Africa.
2. Access to the NHLS material and/or data shall be limited to the minimum required for successful completion of the approved study and shall be made available ***without patient names***.
3. Confidentiality shall be maintained at the participant and institutional level and there shall be no disclosure of personal information or confidential information.
4. The material and/or data obtained from the NHLS shall be anonymised and not, for any reason, be used to track or recruit patients as no pre-approval/consent is obtained from patients.
5. Processes shall be discussed with the relevant NHLS departments (i.e. Corporate Data Warehouse (CDW), NHLS Laboratory Management, Operations Office, etc.) and agreed upon.
6. Any amendments to the study requirements, including the use of the material and/or data for purposes not initially disclosed to the NHLS) shall be cleared by an approved HREC and submitted to the NHLS for approval via the AARMS system – https://aarms.nhls.ac.za.
7. The NHLS shall be acknowledged as a source of material and/or data in any output, such as abstracts and journal articles, emanating from the project.
8. A final report of the research study and any published output resulting from this study shall be submitted to the NHLS via AARMS

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. The NHLS entities tasked with providing the material and/data may have additional requirements for access. Data related queries may be directed to NHLS CDW, email: zarina.sabat@nhls.ac.za; contact number: 011 386 6074 and sample related queries (if applicable) shall be directed to the relevant business manager.

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

APPENDIX 8: NDOH PERMISSION FOR STUDY

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Private Bag X828, PRETORIA, 0001 Dr AB Xuma Building1112 Voortrekker Road, Pretoria Townlands 351-JR, PRETORIA, 0187 email Sandhya.Singh@health.gov.za

The Chairperson
Wits Health Research Ethics Committee
University of Witwatersrand

PERMISSION TO UNDERTAKE RESEARCH AT THE DEPARTMENT OF HEALTH: LEIGH JOHNSTON, MSC FIELD EPIDEMIOLOGY

Dear Chairperson

On behalf of the National Department of Health (NDoH), Directorate: Chronic Diseases, Disability and Geriatrics in the Cluster: Non-communicable Diseases (NCDs), you are hereby informed that Ms Johnston is placed in the Directorate and we are aware, and supportive of the research project proposed by Ms Johnston, a MSc Field Epidemiology student from the University of Witwatersrand and a South African Field Epidemiology Programme (SAFETP) resident, titled:

"Determinants of sub-optimal glycaemic control among patients enrolled in a medicine dispensing programme in Kwazulu-Natal: A longitudinal study, 2014-2021".

As the Director of the National Department of Health's Non-Communicable Diseases Cluster, I hereby grant Ms Johnston permission to conduct her research at the Department of Health as part of her residency. Her research will be conducted and completed between April 2022 and December 2023. She will be accessing secondary data from the Central Chronic Medicine Dispensing and Distribution (CCMDD) programme, situated in the National Health Insurance (NHI) Branch at the National Department of Health, as well as from the National Health Laboratory Service (NHLS). We have fully reviewed her protocol and she has our full support in accessing these data bases to answer questions of percentages of those controlled for their diabetes within the CCMDD as well as determining sub-groups that may be at increased risk for sub-optimal glycaemic control within the CCMDD.

Within a context of poor surveillance and management of Non-Communicable Diseases in the country, the Directorate is encouraged that Ms. Johnston's work will contribute significantly to health system strengthening. Ms Johnston will share the outcomes from her research with our directorate through her manuscript and by presenting her findings at a formal NDoH NCD meeting.

You are most welcome to contact me at sandhya.singh@health.gov.za or telephonically on 0828825012.

Yours sincerely,

S A Singh

Sandhya A Singh
Director: Chronic Diseases, Disabilities and Geriatrics
Cluster: Non-Communicable Diseases
National Department of Health
Date: 25/03/2022

APPENDIX 9: JOURNAL GUIDELINES

Original Research Articles

An original research article presents innovative research within the focus and scope of the journal, according to a clear and well-structured format. Detailed instructions are given below on the structure and contents required. The introduction should argue for the social and scientific value of the research and end with the aim and objectives of the study. Any conceptual or theoretical framework can also be included in the introduction. The methods section should be structured according to the following sub-headings: study design, setting, study population and sampling strategy, intervention (if appropriate), data collection, and data analysis. Occasionally a different structure may be required, for example, in quality improvement or participatory action research. The methods should be followed by a section on ethical considerations. After this, the results are presented. The article should end with a discussion section that summarises the key findings, and then discusses these findings, the strengths and limitations of the study, and any implications or recommendations. This should be followed by a conclusion, acknowledgements and references sections.

Submission status	open
Manuscript language	English or French are considered
Word limit	3500-7000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Aim, Setting, Methods, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, **Ethical Clearance/Waiver Documentation** and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

AOSIS Publishing

AOSIS Publishing house style for authors

Manuscripts must adhere to the following guide before submission.

Table of content

Physical Address: 15 Oxford Street, Durbanville, 7550.
Postal Address: Postnet Suite 110, Private Bag X19, Durbanville, 7551.
Phone: 086 1000381 or +27 21 975 2602 | Fax: +27 21 975 4635 | Email: info@aosis.co.za | URL: www.aosis.co.za
African Online Scientific Information Systems (Pty)Ltd t/a AOSIS Reg No: 2002/002017/07

Language usage

General elements

- **Quotations:** Use single quotation marks for quotations. For quotations within quotations, use double quotation marks. Quotations of more than 30 words are to be indented. Do not use quotation marks for indented quotations unless it is direct speech (e.g. interviewee responses).
- **En dashes and hyphens:** Use an en dash (i.e. extended hyphen that can be found in the Insert box under Symbols in Microsoft Word) in ranges of numbers and dates. Use hyphens only for words that are hyphenated.
- **Dates:** Format dates as '02 October 2006', except at the beginning of sentences where numerals and dates should either be spelt out or the sentence should be rearranged.
- **Percentage:** The per cent symbol (%) is used in conjunction with all numbers (e.g. 12%). Numbers that have been written out will appear with 'percent' (e.g. five percent). 'Percentage' is used in a general sense.
- **Numbers:** Numbers from one to nine must be written out. Numbers from 10 onwards, must be used as numerals, except at the beginning of a sentence.
- **Spacing and punctuation:** There should be one space (and not two) between sentences; one space before unit terms (e.g. 5 kg, 5 cm, 5 mmol, 5 days, 5 °C, etc.), but no space before the percentage symbol (%). Thousands and millions are marked with a space and *not* a comma (e.g. 1000, 1 000 000). Ranges are expressed with an extended hyphen (i.e. en dash), not with a short hyphen (e.g. 1990–2000).
- **Units:** The use of units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as in the decimal point (not the decimal comma), and the 24-hour clock.
- **Foreign language:** Foreign language words should be italicised, unless these words are part of normal usage. Consult the Oxford English Dictionary if in doubt.
- **Acronyms:** If a phrase with an established acronym or abbreviation is used and appears more than five times in your manuscript, please include the acronym or abbreviation in brackets after first mention of the phrase, and then use the acronym or abbreviation only. Please note that you should not define acronyms or abbreviations in any of your headings. If either has been used in your abstract, you need to define them again on their first usage in the main text.

Sensitive and political terms

- **Race and ethnicity**: Try to avoid terms such as 'blacks' and 'whites'; use instead 'black *people*', 'white *people*', etc. 'Caucasian', 'Mongoloid', 'Negroid', etc. are generally to be avoided except in human population studies. 'Mixed race' is preferable to 'half-caste' or 'coloured'.
- **Disabilities:** Avoid using 'the disabled', 'the handicapped', and instead use 'people with disabilities not 'the disabled' or 'people with learning difficulties', not 'mentally handicapped'.
- **Disease**
    - Avoid health-determined categorisation.
        - Use 'people with diabetes'; not 'diabetics'.
        - Use 'people with cancer'; not 'cancer sufferers'.

    - Use 'sexually transmitted infection (STI)' and not 'sexually transmitted disease (STD)'.
  - Avoid phrasing that dehumanises a patient. Many authors use case (instance of a disease) when they mean patient (i.e. the person or individual who is ill with the (disease).
- **AIDS**
  - Ensure that 'AIDS' is used for the disease and 'HIV' for the virus, e.g. do not use 'AIDS carrier', 'AIDS positive', 'AIDS virus' or 'catching AIDS or HIV/AIDS' (avoid using the solidus here).
  - 'AIDS sufferer/victim' is inappropriate; use 'people with AIDS'.
  - Refer to 'people who practise high-risk activities' and not '*high-risk groups*'.
  - The expression 'full-blown AIDS' is unnecessary if the correct distinction has been made between HIV and AIDS.
- **Male versus Female**
  - 'Male' and 'female' are *adjectives*, so be careful to use them as such (i.e. a *male* patient and a *female* frog, but a 35-year-old *man*, a French *woman* and a group of 25 *men* and 35 *women*).
- **Sexuality:** Avoid the terms '*homosexual activities*' (if achievable within the manuscript's context, specify which activity is being referred to, especially when dealing with medical research.) Avoid using '*homosexuals*' (specify homosexual men or homosexual women).
- **Gender:** Use gender neutral nouns. Avoid the use of 'man' if not specifically referring to men; for example:
  - for 'man' use 'humans'
  - for 'man-kind' use 'the human race'
  - for 'man-power' use 'workforce'
  - for 'man-made fibre' use 'synthetic fibre'
- **'He/she', 'him/her' and 'his/hers':** For 'he/she', 'him/her' and 'his/hers' rather use 'he or she', 'her or him', 'his or hers' (without a solidus) or change to plural 'they'. Use inclusive pronouns: use 'he or she', or rephrase the sentence (rephrasing to the plural form often works):

✗ ... *Any observer* of changes in publishing technology will perceive that *he* has need of...

✓ ... ***Observers*** of... will perceive that *they* have...

Beware of referring to people with stereotypical pronouns (e.g. 'the doctor treated *his* patient'; 'the secretary tidied *her* desk').

- **Geography**
  - The terms *Third World*, *poor countries* and *underdeveloped countries* should be avoided.
  - *Developing* or *non-developed country/society* is better, but it is best to specify countries or regions instead.
  - *Western society* and *Western World* should only be used in relation to geography; otherwise, use *developed world/society* or, even better, specify the countries themselves or the region.

Tables, figures and photographs

Tables should in an Excel (.xls) format. Ensure that all personal identifying information is removed from the supplementary files as indicated in the provided instructions. All captions should be provided together on a separate page. Tables and figures should use numerical numbers.

- **Organise your visual presentation**: Once you have read through the analyses and decided how best to present each table or figure, think about how you will arrange them within the manuscript. The analyses should tell a story' that leads the reader through the steps needed to logically answer the question(s) that you as author are posing in the Introduction. The order in which you present the results can be as important in convincing the readers as what you actually are saying in the text.
- **How to refer to tables and figures in the text:** Every figure and table included in the paper *must* be referred to in the body of the text. Use sentences that draw the reader's attention to the relationship or trend you wish to highlight, referring to the appropriate figure or table only in parenthesis e.g.:
    - Germination rates were significantly higher after 24 h in running water than in controls (Figure 4).
    - DNA sequence homologies for the purple gene from the four congeners (Table 1) show high similarity, differing by at most 4 base pairs. (Avoid sentences that give no information other than directing the reader to the figure or table, e.g. Table 1 shows the summary results for male and female heights at Bates College.)
- **Abbreviation of the word 'Figure':** When referring to a figure in the text, the word 'figure' is never abbreviated as 'Fig.'; the same rule applies to the usage of 'table'. Both words are spelled out completely in descriptive legends.
- **How to number tables and figures:** Figures and tables are numbered independently, in the sequence in which you refer to them in the text, starting with Figure 1 and Table 1. If, in revision, you change the presentation sequence of the figures and tables, you must renumber them to reflect the new sequence.
- **The acid test for tables and figures:** Any table or figure you present must be clear, well-labelled, and described by its legend to be understood by your intended audience without reading the results section. That is, it must be able to stand alone and be interpretable. Overly complicated figures or tables may be difficult to understand in or out of context, so strive for simplicity whenever possible.
- **Descriptive legends or captions:** To pass the acid test above, a clear and complete legend (sometimes called a caption) is essential. Like the title of the manuscript itself, each legend should convey as much information as possible about what the table or figure intends to tell the reader:
    - the results that are being shown in the graph(s), including the summary statistics plotted
    - the organism studied in the experiment (if applicable)
    - a context for the results: the treatment applied or the relationship displayed, etc.
    - location (*only* if a field experiment)
    - specific explanatory information needed to interpret the results shown (in tables, this is frequently done as footnotes)
    - culture parameters or conditions if applicable (temperature, media, etc.)

- sample sizes and statistical test summaries, as they apply

Do not simply restate the axis labels with a 'versus' written in between.

Example: Figure 1: Height frequency (%) of White Pines (Pinusstrobus) in the Thorncrag Bird Sanctuary, Lewiston, Maine, before and after the Ice Storm of 1998. Before, *n* = 137, after, *n* = 133. Four trees fell during the storm and were excluded from the post-storm survey.

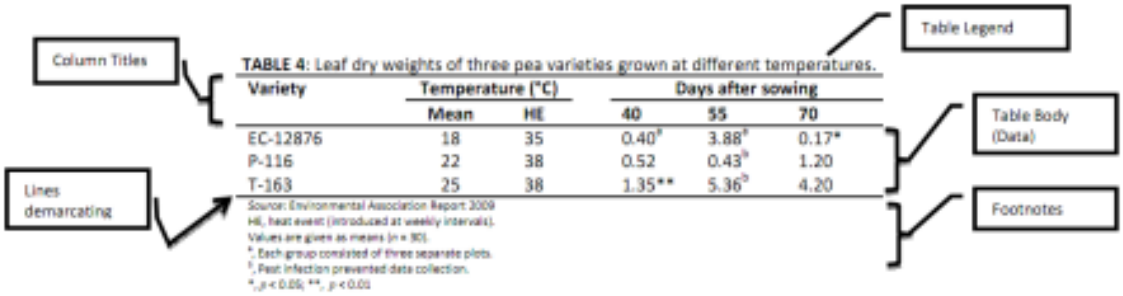


TABLE 4: Leaf dry weights of three pea varieties grown at different temperatures.

Variety	Temperature (°C)		Days after sowing		
	Mean	HE	40	55	70
EC-12876	18	35	0.40[a]	3.88[a]	0.17*
P-116	22	38	0.52	0.43[b]	1.20
T-163	25	38	1.35**	5.36[b]	4.20

Source: Environmental Association Report 2009
HE, heat event (introduced at weekly intervals).
Values are given as means (*n* = 30).
[a], Each group consisted of three separate plots.
[b], Pest infection prevented data collection.
*, $p < 0.05$; **, $p < 0.01$

Note: Questions frequently arise about how much methodology to include in the legend, and how much results reporting should be done. For laboratory reports, specific results should be reported in the results text with a reference to the applicable table or figure. Other than culture conditions, methods are similarly confined to the Methods section.

Footnotes to tables, figures and photographs

Do not introduce footnotes in the body of the manuscript. Footnotes should be used as follows:

- Copyright and permissions to reproduce should be clearly stated.
- Notes about the table as a whole can be left unlinked (i.e. no linking letters or numbers or symbols) or linked to, for example, a relevant column heading.
- Notes about specific parts of the table should be linked using superscript lower case letters (preferred), superscript numbers or symbols.
- If lower case letters are used, it could be confused with the table data; use symbols or numbers instead.
- Do not make use of superscript numbers in parentheses (brackets).
- If an abbreviation is mentioned for the first time in a table (e.g. 'CE' in Table 1), it must be defined in a footnote to that table, (e.g. HE, Heat event (introduced at weekly intervals).
- Asterisk footnotes are reserved for probability values in tables and usually signify the following values: *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$. The asterisk is often used in mathematics and should therefore be avoided as a footnote symbol.
- Footnote links should be placed after punctuation. The preferred order of footnote symbols in tables (which should be superscripted) is †, ‡, §, ¶ (these are doubled if more footnotes are needed, e.g. ††).
- When superscript numbers or letters are used in text, beware of potential confusion with other superscripts (e.g. 2 for 'squared').
- Footnotes should be in the following order:

- source notes
- other general notes
- notes on specific parts of the table (following the order in the table itself)
- notes on level of probability

Guidance on submitting creatives electronically

Please supply images as the size intended for final publication. Resizing of images is time consuming and can result in loss of quality.

Supply your manuscript creatives in one of the following three preferred formats:

- **TIFF:** This is an image made up of pixels and is the most universal and most widely supported format across Windows and Mac platforms. Most graphics packages can save a file as a TIFF. The higher the resolution (i.e. the number of pixels) the sharper the final image.
  - Colour or greyscale photographic images: 300dpi
  - Line art or combination images: 600/900dpi
  - We would recommend using this format for photographic images.
- **EPS**: An EPS is essentially an envelope for holding text and images. Line art can be produced as an EPS (in Illustrator, for example). There are virtually no limits to scaling line art saved as an EPS. It can also contain TIFF images. However, please ensure that all fonts are embedded (that is, saved as outlines) and that line weights are not defined as hairline.
- **PDF**: This format is, again, like an EPS in that it is an envelope for holding different kinds of images and line art. Great care should be taken to ensure that fonts are embedded and that original images are at the correct size and resolution before being saved as a PDF. It is possible to save or export as TIFF or EPS from most graphics applications, just as it is possible to save direct to a PDF from most graphics packages by using a postscript printer driver. PDF creation packages (e.g. Acrobat Distiller) are also now widely available.

Other file formats

- **JPEG**: A JPEG compressed TIFF is acceptable as long as the degree of compression is moderate. It is better to use a JPEG for online images as a good quality image is achievable even with a high degree of compression.
- **GIF**: A format suitable for images that contain few colours. Again, this should only be used for images intended for the web.
- We cannot guarantee the quality of images supplied in other formats.

Colour:

- *Greyscale, CMYK, RGB.*
- **Greyscale** art should be saved in greyscale mode.
- **C**yan**M**agenta**Y**ellow**B**lack are the base colours used during the printing process.
- Any colour that is to appear in print must be in CMYK mode.
- **R**ed**G**reen**B**lue are the colours used by monitors and default scanner settings. Any colour that is to appear online must be in RGB mode.

Guidelines for Math

- Set display equations in MathType. Each display equation should be in its own MathType object. Each MathType object should contain the entire equation, including final punctuation. The equation number should be set as Microsoft Word regular text, outside the MathType object, separated by either a tab or a space.
- Set in-text (inline) math in Microsoft Word regular text. Exception: If in-text (inline) math has elements that should be stacked or have rules, circumflexes, arrows, or other accents spanning over more than one character, set in MathType as 'Inline Equation.'
- If any characters cannot be found in Word's Symbol palette ('(normal text),' 'Times New Roman,' or 'Symbol'), please set in MathType.
- No display equations are allowed in figure captions, table titles, or table footnotes. If a display equation occurs in a text footnote, it is best to recast it as inline math. There are a few journals with lengthy footnotes with style exceptions to this rule.
- No numbered equations are allowed in table footnotes.
- Display and/or numbered equations ARE allowed in table body, but must be 'inline' when converted to MathML equations.

Fonts: Unicode fonts

Please use standard (UNIcode) fonts such as Palatino, Times New Roman, Helvetica and Symbol. Fonts that have not been embedded will usually be replaced by Courier, resulting in character loss or realignment.

Understanding Unicode

The explanation at Unicode.org is a good place to begin.

'Unicode provides a unique number for every character, no matter what the platform, no matter what the program, no matter what the language.' (Unicode.org, 2011)

Put more simply, no matter what font is used, your computer and other computers will always know exactly what symbol is called for and display the text correctly.

Note: AOSIS Publishing publishes in four different formats, namely, PDF, HTML, XML and ePUB. If your manuscript is not unicode compliant, then it will not be possible to produce all four formats. We will send the back to you to make the fonts Unicode compliant to enable us to produce all four formats.

How to check whether your font-type is unicode compliant

1. Open your manuscript in your text editor.
2. Highlight all the text within your manuscript and change the font to Arial or Times New Roman.
3. Scrutinise your entire manuscript.
    - **Document reads perfectly?** If the words are readable and identifiable, then the font that you are using is unicode compliant.
    - **Document has changed certain or all characters?** Font used is not unicode compliant and needs to be changed prior to submission to this journal.

Which fonts are Unicode compliant?

- To use Unicode, you will need to install (or find already installed) Unicode fonts on your computer. This is neither difficult nor costly.
- For basic information and links to numerous Unicode fonts, see http://www.alanwood.net/unicode/fonts.html
    - Arial Unicode MS
    - Courier New
    - DejaVu Serif
    - Gentium
    - Garamond
    - Minion Pro
    - Myriad Pro
    - Tahoma
    - Times New Roman
    - Verdana

Unicode in Windows

Installing fonts on a Windows computer is fairly simple.

1. Download the font.
2. If it is a compressed file (such as .zip), expand it.
3. Open the fonts folder by clicking on Start, then Settings, then Control Panel, then Fonts.
4. Drag the font file(s) into this folder. It should automatically install.

Using the Insert symbol function

- Use the Insert Symbol function (found in the Insert menu). This function allows you to choose characters from a grid displayed in its own window. Double-clicking the desired character inserts it at the cursor in the document.
- Use the symbol insert window to assign keystrokes to the characters you use most often. For example, you might assign the keystroke alt+a to the lower case a with macron, and alt+shif+A to capital A with macron.

Keyboard for Windows

The preferred method for typing in Unicode. Essentially this means telling Windows that you want a different keyboard layout to be available for use. At this step things might vary from computer to computer.

- Click on Start, then Settings, then Control Panel.
- Double click Regional and Language Options. The window that opens should have three tabs: Regional Options, Languages, and Advanced.
- Click on the Keyboards and Languages tab.
- Options include installing additional languages or changing the keyboard. Read the guidelines provided by Windows carefully.
- Select 'Change keyboards' in the same window after installing additional language.
- To make it your default keyboard you must choose it in the drop down list under Default Input Language at the top of this window. Click Add.
- Proceed to select the 'Language Bar' tab at the top and ensure that the box 'Show additional Language bar icons in the taskbar' is ticked.

- Now there should be a little keyboard icon in the task bar at the bottom of your screen (if there wasn't already). (It will be next to the blue square with EN in it, which signifies that the current input language is English. If you use no other languages, this icon might not be there.) When you click on the small keyboard icon, a list of keyboard choices pops up. If you made Alt-Latin the default, it should be in bold type. (However, it may not appear until the next time you restart your computer. Until then it might be a blank line in the list.)

Typing with the alternative keyboard is simple. For most letters you will do things as you always have. When you need a special character or a character with a diacritic or accent, you will use key combinations with the Alt key to the right of the space bar (the one on the left side does not work for this in Windows, unfortunately). For example, to type the letter 'a' with a macron you hold down the Alt key and press the letter a, release them both, then type the letter a. For letters with a dot below them, hold down Alt, press the period key, release both, and then type the letter which needs the dot.

Unicode in Macintosh

To enter Unicode text on a Macintosh, you have several options.
Firstly, you may use the **Character Pallette**, which is found in the Input Menu (the flag menu in the upper right, near the clock).

- If the Character Pallette option is not shown, enable it by doing the following:
  - Go to the Apple menu, select System Preferences.
  - In the Preferences window, choose International.
  - Select Input Menu.
  - Check Character Pallette. You can also check Keyboard Viewer, Unicode Hex Input, and US Extended at this time.
  - Check Alt-Latin. If it is not there, see below for information on installing it.
  - Make sure the "Show Input Menu in menu bar" option is checked.
- To use the Character Pallette to enter Unicode characters in a document, just keep it open in the background. When you need a character, you can enter it by double clicking on it in Character Pallette.
- A useful feature of Character Pallette is the ability to designate frequently-used characters as favourites, saving you the trouble of finding the different letters each time you need them.
- For more information on Character Pallette, see Alan Wood's site: http://www.alanwood.net/unicode/utilities_fonts_macosx.html

Secondly, you may use the excellent and extremely simple **Alt-Latin keyboard** or **LatinTL keyboard**, both of which were created specifically for this purpose by Kino.

- To install either keyboard (or both of them), you must first download AltLatin.zip and/or LatinTL_X.dmg.sit from Alt-Latin page).
- If your browser does not automatically expand the .zip or .sit file, tell it to save the file to your desktop (so it will be easy to find), then manually expand it. Usually this can be done simply by double-clicking the file, which will start the appropriate decompression program. LatinTL expands to a disk image, but for the purpose of installation you can treat it just like a folder.
- Follow the instructions in the 'readme' file to install the keyboard(s).

- Make it visible in the Input Menu by following the instructions given above for the Character Pallette.
- Because Alt-Latin and LatinTL work like any other keyboard, you will not have to change keyboards unless you need to type in a different alphabet, such as Arabic.
- Entering letters with diacritics using either keyboard is very simple:
    1. Make sure you are using a Unicode font. It may work with other fonts, but you should use Unicode (OS X comes with Lucida Grande and there are others available).
    2. To enter a vowel with a macron, simply hold down either **option** key and hit the letter 'a' simultaneously. Release them, then type the letter that needs the macron (using the shift key if you need a capital).
    3. For letters with dots below, press option and period, release, then type the letter.
    4. Hamza is shift+option+P, and 'ayn is option+p. (This may not work in Microsoft Word with Alt-Latin – reason unknown. If it does not work, use the LatinTL keyboard instead, or use the Character Pallette for these two characters. These keystrokes do work in TextEdit and other software with Alt-Latin.)
- The PDF file included with Alt-Latin shows maps of the keyboard, in case you need something not mentioned here, or you may use our maps found on http://www.lib.uchicago.edu/e/collections/mideast/encyclopedia/unicode.html.
- The layout of LatinTL is very similar, with only a few differences, and it also includes maps. (See the Alt-Latin page for a description of the differences.)
- **Click** here **for diagrams of the Alt-Latin keyboard** (usable for LatinTL as well, with a few differences) and for downloads.
- The diagrams are for the Windows version, but the layout is almost identical to the Mac version. The main difference is that where the Windows version uses only the Alt key to the right of the space bar, the Mac version uses either of the two Option keys. This makes the Mac version a little more comfortable to use, since you can use either hand. (There is no Windows version of LatinTL.)
- There are downloadable PDF files of the diagrams available on the same page, in case you would like to print them for easier reference while typing.
- Kino's site (linked above) also has numerous other Macintosh keyboard and font resources, such as some keyboards based on non-US layouts (notably a UK variant of Alt-Latin).

Thirdly, you may want to use Knut S. Vikør's **Jaghbub keyboard layouts** (and, perhaps, his Unicode fonts).
His Arabic Macintosh pages have long been one of the web's most useful sources for Mac users who need to type Arabic or transliteration, and he has updated both the pages and the downloadable resources he created.

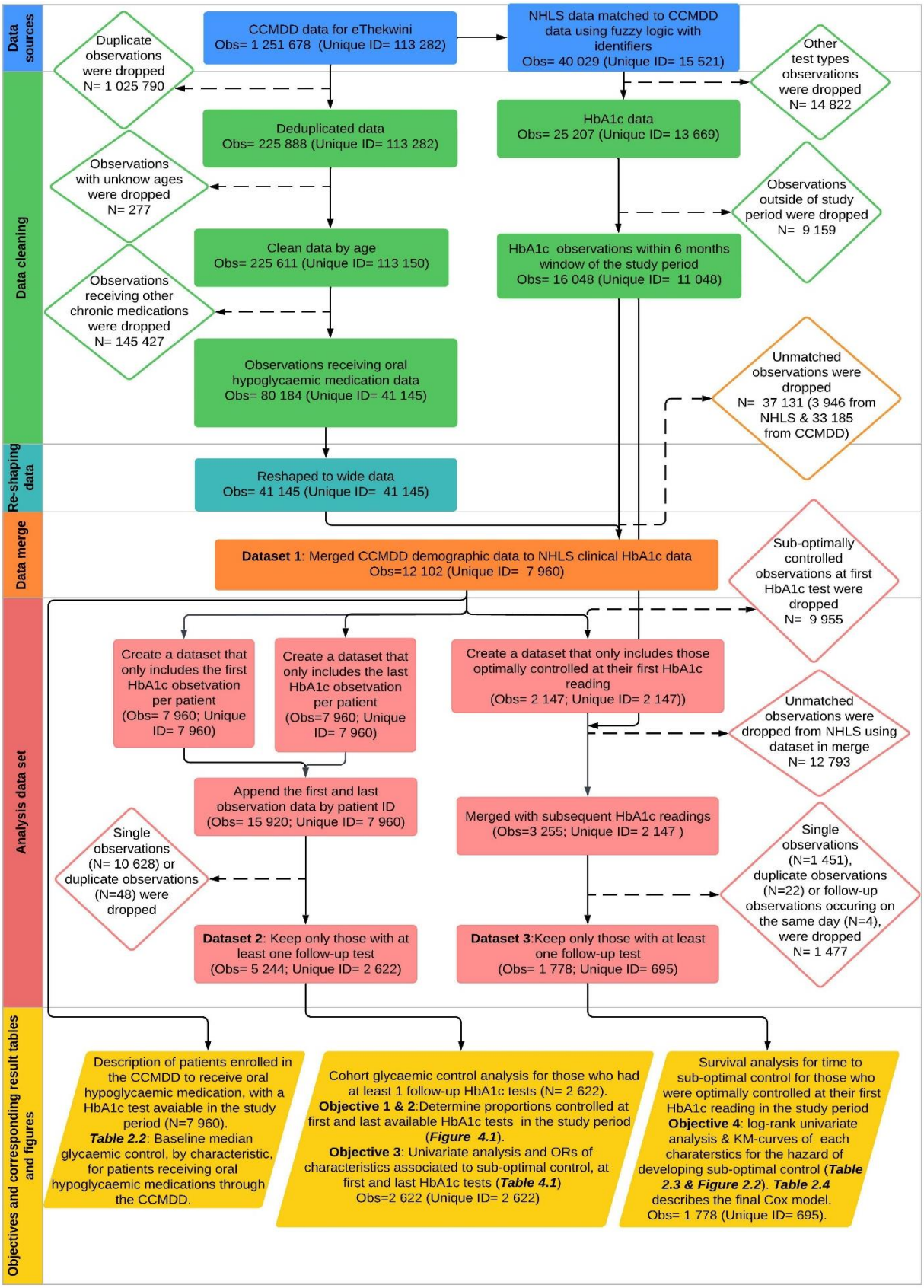
- The page on transliteration, 'Writing Arabic with Latin letters', explains the issues and provides a downloadable file containing the JaghbUni font package and the American Diacs. keyboard layout.
- The Jaghbub font package page gives more information about the three fonts included, as well as German, French, Italian, Danish, Swedish, Norwegian, US and UK keyboard layouts for typing diacritics in Unicode fonts.
- There are also separate keyboard layouts for typing IPA characters in Unicode fonts for the same national standards (that is, the non-option keys

follow the regular national keyboard standard, but the IPA characters are all placed on option keys under no particular standard).

For any keyboard layout, you can always select **Keyboard Viewer** from the Input Menu to see what different keystrokes will do.

These instructions were taken from:
http://www.lib.uchicago.edu/e/collections/mideast/encyclopedia/unicode.html

APPENDIX 10: DATA MANAGEMENT FLOW DIAGRAM



APPENDIX 11: TABLE OF THE DESCRIPTIVE CHARACTERISTICS FOR THE COHORT STUDY PARTICIPANTS

Baseline median HbA1c value by patient characteristic for the Central Chronic Medicines Dispensing and Distribution programme cohort receiving oral hypoglycaemic medication for T2DM, with ≥ 1 repeat HbA1c test available, eThekwini, KZN, South Africa: 19th April 2018-30th Dec 2021 (N = 2622).

Characteristic	Total N=2622 (100%) % (n/N)	Median HbA1c (IQR)	Sub-optimal (HbA1c >7%) N=1927 (73.5%) % (n/N)	Optimal (HbA1c ≤7%) N=695 (26.5%) % (n/N)	p-value[†]
Gender					0.032[*]
Male	32% (850/2 622)	8.0 (6.9–9.9)	31% (602/1 927)	36% (248/695)	
Female	68% (1 772/2 622)	8.3 (7.0–10.1)	69% (1 325/1 927)	64% (447/695)	
Age (years)					<0.001[***]
≤39 year	4% (113/2 622)	8.6 (7.2–11.3)	5% (89/1 927)	3% (24/695)	
40–59 years	49% (1 286/2 622)	8.5 (7.1–10.5)	51% (988/1 927)	43% (298/695)	
60–79 years	44% (1 152/2 622)	7.9 (6.9–9.6)	43% (819/1 927)	48% (333/695)	
≥80 years	3% (71/2 622)	6.9 (6.5–7.6)	2% (31/1 927)	6% (40/695)	
Type of facility					0.42
PHC facility[a]	70% (1 840/2 622)	8.2 (7.0–9.9)	70% (1 344/1 927)	71% (496/695)	
Hospital	30% (782/2 622)	8.2 (7.0–10.3)	30% (583/1 927)	29% (199/695)	
T2DM-related complication					0.016[*]
Neuropathy or nephropathy	50% (1 320/2 622)	8.0 (6.9–9.9)	49% (943/1 927)	54% (377/695)	
None recorded	50% (1 302/2 622)	8.3 (7.1–10.1)	51% (984/1 927)	46% (318/695)	
Type of therapy					<0.001[***]
Monotherapy	52% (1 360/2 622)	7.6 (6.7–9.4)	45% (876/1 927)	70% (484/695)	
Dual-therapy	48% (1 259/2 622)	8.7 (7.4–10.6)	54% (1 048/1 927)	30% (211/695)	
Triple-therapy	0% (3/2 622)	9.5 (9.0–10.1)	0% (3/1 927)	0% (0/695)	
Comorbidity					0.098
T2DM[b] alone	15% (390/2 622)	9.0 (7.2–10.5)	16% (304/1 927)	12% (86/695)	
T2DM and HIV[c]	6% (161/2 622)	8.6 (7.1–10.6)	6% (122/1 927)	6% (39/695)	
T2DM and HPT[d]	68% (1 791/2 622)	8.0 (7.0–9.8)	68% (1 301/1 927)	71% (490/695)	
T2DM, HIV and HPT	10% (275/2 622)	8.2 (6.9–10.1)	10% (195/1 927)	12% (80/695)	
T2DM and dyslipidaemia	0% (5/2 622)	10.1 (8.6–10.5)	0% (5/1 927)	0% (0/695)	

[a]Primary health care, [b]Type two diabetes mellitus, [c]Human Immunodeficiency Virus, [d]Hypertension; [†]p-value for the chi-square test for sub-optimal vs optimal; Significance level (p-value): [*]p<0.05, [**]p<0.01, [***]p<0.001.